Hines, J.
09/210995

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-key Terms

L1 (5032) SEA FILE=CAPLUS ABB=ON PLU=ON (HEMOPHIL? OR HAEMOPHIL? OR H)(W)INFLUENZ? OR NTHI OR OTITIS MEDIA
L2 (55) SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND ((HMW OR HMP)(S)MOLECUL? OR HIGH(1W)(WEIGHT OR WT))
L3 28 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND (ANTIGEN OR ADHESIN OR HNI47 OR HNI 47 OR HSP OR HEAT(W)SHOCK)

=> d 1-28 .beverly

L3 ANSWER 1 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1999:75537 CAPLUS
TI A putative **adhesin** gene cloned from Campylobacter jejuni
SO Res. Microbiol. (1998), 149(10), 723-733
CODEN: RMCREW; ISSN: 0923-2508
AU Kelle, K.; Pages, J.-M.; Bolla, J.-M.
PY 1998
AB Thirteen Campylobacter jejuni strains of human origin showed differing behaviors when analyzed for their ability to bind the Caco-2 cell line in vitro, suggesting variations in genetic complements and/or regulation. We designed an oligonucleotide probe corresponding to a highly conserved part of **adhesins** from various Gram-neg. bacteria. Among our lab. collection, Southern hybridization has demonstrated that only a discrete no. of strains harbor this sequence. The corresponding gene has been cloned from our prototype strain and sequence anal. has confirmed homol. with Gram-neg. bacterial **adhesins**. The ORF corresponded to 869 amino acids; we named this protein P95. Protein sequence similarity

assessment demonstrated that this gene product belongs to the family of proteins including the filamentous haemagglutinin of Bordetella pertussis and the **high**-mol.-**wt**. surface-exposed **adhesins** of **Haemophilus influenzae**. Comparison of adhesion and hybridization results emphasized the involvement of this gene in an essential pathogenic process of Campylobacter.

L3 ANSWER 2 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1999:25012 CAPLUS
TI Characterization of emb, a gene encoding the major **adhesin** of Streptococcus defectivus
SO Infect. Immun. (1999), 67(1), 50-56
CODEN: INFIBR; ISSN: 0019-9567
AU Manganelli, Riccardo; Van De Rijn, Ivo
PY 1999
AB Streptococcus defectivus is one of the nutritionally variant streptococci, a class of viridans group streptococci first isolated from patients with endocarditis and **otitis media** . In previous studies, NVS-47, a clin. isolate of S. defectivus, was shown to bind to the extracellular matrix. A **high** -mol.-**wt**. surface protein was identified and proposed to be responsible for mediating this binding. In the present study, the gene encoding this protein was identified by transposon mutagenesis and characterized. The gene (emb) was found to be larger than 14 kb and was partially sequenced. It encodes a protein contg. at least 50 repeats of 77 amino acids predicted to assume an alternating coiled-coil conformation. The domain responsible for extracellular matrix binding was mapped to the N terminus of the protein. From sequence anal., Emb is proposed to be the prototype of a new family of streptococcal fibrillar proteins.

L3 ANSWER 3 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1998:604694 CAPLUS
DN 129:242430
TI A **high** molecular **weight** major outer membrane protein of Moraxella and the gene encoding it
SO U.S., 34 pp. Cont.-in-part of U.S. Ser. No. 431,718.
CODEN: USXXAM
IN Sasaki, Ken; Harkness, Robin E.; Loosmore, Sheena M.; Klein, Michel H.

	APPLICATION NO.	DATE
AI	US 95-478370	19950607
	WO 96-CA264	19960429
	CA 96-2219889	19960429
	AU 96-53941	19960429
	EP 96-910872	19960429
	JP 96-532876	19960429

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5808024	A	19980915	US 95-478370	19950607
	WO 9634960	A1	19961107	WO 96-CA264	19960429
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	CA 2219889	AA	19961107	CA 96-2219889	19960429
	AU 9653941	A1	19961121	AU 96-53941	19960429
	EP 826052	A1	19980304	EP 96-910872	19960429
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11502415	T2	19990302	JP 96-532876	19960429
PY	1998				
	1996				
	1996				
	1996				
	1998				
	1999				

AB An outer membrane protein of Moraxella strain, particularly M. catarrhalis, with a mol. mass of about 200,000 is characterized and the gene encoding it is cloned. The protein and the gene encoding it are useful in diagnostic applications and in vaccines against Moraxella infections, e.g. against **otitis media** and lower respiratory tract infections. The protein was identified as one present in clumping strains of M. catarrhalis but absent from non-clumping ones. Patients recovering from **otitis media** had antibodies to the protein. The protein was partially purified by gel electrophoresis and antibodies raised against it. The antibodies were used to screen a Sau3A partial digest expression library to obtain the gene.

L3 ANSWER 4 OF 28 CAPLUS COPYRIGHT 1999 ACS

AN 1998:296924 CAPLUS

DN 129:39889

TI Nasopharyngeal colonization with nontypeable **Haemophilus influenzae** in chinchillas

SO Infect. Immun. (1998), 66(5), 1973-1980
CODEN: INFIBR; ISSN: 0019-9567

AU Yang, Yan-Ping; Loosmore, Sheena M.; Underdown, Brian J.; Klein, Michel H.

PY 1998

AB Colonization of the nasopharynx by a middle ear pathogen is the first step in the development of **otitis media** in humans. The establishment of an animal model of nasopharyngeal

colonization would therefore be of great utility in assessing the potential protective ability of candidate vaccine **antigens** (esp. **adhesins**) against **otitis media**. A chinchilla nasopharyngeal colonization model for nontypeable **Haemophilus influenzae** (**NTHI**) was developed with antibiotic-resistant strains. This model does not require coinfection with a virus. There was no significant difference in the efficiency of **NTHI** colonization between adult (1- to 2-yr-old) and young (2- to 3-mo-old) animals. However, the incidence of middle ear infection following nasopharyngeal colonization was significantly higher in young animals (83 to 89%) than in adult chinchillas (10 to 30%). Chinchillas that had recovered either from a previous middle ear infection caused by **NTHI** or from an infection by intranasal inoculation with **NTHI** were completely protected against nasopharyngeal colonization with a homologous strain and were the best pos. controls in protection studies. Systemic immunization of chinchillas with inactivated whole-cell prepns. significantly protected animals not only against homologous **NTHI** colonization but also partially against heterologous **NTHI** infection. In all protected animals, significant serum anti-P6 and anti-HMW antibody responses were obsd. The outer membrane P6 and **high-mol.-wt.** (**HMW**) proteins appear to be promising candidate vaccine **antigens** to prevent nasopharyngeal colonization and middle ear infection caused by **NTHI**.

L3 ANSWER 5 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1998:296912 CAPLUS
DN 129:53186
TI Synthesis and characterization of lipooligosaccharide-based conjugates as vaccine candidates for Moraxella (Branhamella) catarrhalis
SO Infect. Immun. (1998), 66(5), 1891-1897
CODEN: INFIBR; ISSN: 0019-9567
AU Gu, Xin-Xing; Chen, Jing; Barenkamp, Stephen J.; Robbins, John B.; Tsai, Chao-Ming; Lim, David J.; Battey, James
PY 1998
AB Moraxella (Branhamella) catarrhalis is an important cause of **otitis media** and sinusitis in children and of lower respiratory tract infections in adults. Lipooligosaccharide (LOS) is a major surface **antigen** of the bacterium and elicits bactericidal antibodies. Treatment of the LOS from strain ATCC 25238 with anhyd. hydrazine reduced its toxicity 20,000-fold, as assayed in the Limulus amebocyte lysate (LAL) test. The detoxified LOS (dLOS) was coupled to tetanus toxoid (TT) or **high-mol.-wt.** proteins (**HMP**) from nontypeable **Haemophilus influenzae** through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-

HMP. The molar ratios of dLOS to TT and HMP conjugates were 19:1 and 31:1, resp. The antigenicity of the two conjugates was similar to that of the LOS, as detd. by double immunodiffusion. S.c. or i.m. injection of both conjugates elicited a 50- to 100-fold rise in the geometric mean of IgG to the homologous LOS in mice after three injections and a 350- to 700-fold rise of anti-LOS IgG in rabbits after two injections. The immunogenicity of the conjugate was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced antisera had complement-mediated bactericidal activity against the homologous strain and heterologous strains of M. catarrhalis. These results indicate that a detoxified LOS-protein conjugate is a candidate for immunization against M. catarrhalis diseases.

L3 ANSWER 6 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1998:7848 CAPLUS
DN 128:138477
TI Prevalence and distribution of the hmw and hia genes and the HMW and Hia **adhesins** among genetically diverse strains of nontypeable **Haemophilus influenzae**
SO Infect. Immun. (1998), 66(1), 364-368
CODEN: INFIBR; ISSN: 0019-9567
AU St. Geme, Joseph W., III; Kumar, Vini V.; Cutter, David; Barenkamp, Stephen J.
PY 1998
AB Nontypeable **Haemophilus influenzae** is a common cause of human disease and initiates infection by colonizing the upper respiratory tract. In previous work we identified **high**-mol.-**wt. adhesins** referred to as HMW1 and HMW2, expressed by nontypeable strain 12, and detd. that most strains of nontypeable **H. influenzae** express one or two antigenically related proteins. More recently, we detd. that some strains lack HMW1- and HMW2-like proteins and instead express an **adhesin** called Hia. In the present study, we detd. the prevalence and distribution of the hmw and hia genes in a collection of 59 nontypeable strains previously characterized in terms of genetic relatedness. Based on Southern anal., 47 strains contained sequences homologous to the hmw1 and hmw2 genes and nine strains contained homologs to hia. No strain harbored both hmw and hia, and three strains harbored neither. Although the hmw and hia genes failed to define distinct genetic divisions, the hmw-deficient strains formed small clusters or lineages within the larger population structure. Addnl. anal. established that the IS1016 insertion element was uniformly absent from strains contg. hmw sequences but was present in two-thirds of the hmw-deficient strains. As IS1016 is assocd. with the capsule locus (cap) in most encapsulated strains of **H. influenzae**, we speculate that hmw-deficient nontypeable strains evolved more recently from an encapsulated ancestor.

Searcher : Shears 308-4994

L3 ANSWER 7 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1997:679100 CAPLUS
DN 127:345324
TI **High** molecular **weight** surface proteins of non-typeable Haemophilus
SO PCT Int. Appl., 182 pp.
CODEN: PIXXD2
IN Barenkamp, Stephen J.

APPLICATION NO.	DATE
WO 97-US4707	19970401
AU 97-25873	19970401
EP 97-917597	19970401

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9736914	A1	19971009	WO 97-US4707	19970401
AU 9725873	A1	19971022	AU 97-25873	19970401
EP 900232	A1	19990310	EP 97-917597	19970401

PI
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PY 1997
1997
1999

AB **High** mol. **wt**. surface proteins of non-typeable **Haemophilus influenzae** which exhibit immunogenic properties and genes encoding the same are described. Specifically, genes coding for two immunodominant **high** mol. **wt**. proteins, HMW1 and HMW2, have been cloned, expressed and sequenced, while genes coding for high mol. proteins HMW3 and HMW4 have also been cloned, expressed and sequenced. These proteins, epitopes, or conjugates with other **antigen**, hapten, or polysaccharide are useful for eliciting immune response to protect against **Haemophilus influenza** type b.

L3 ANSWER 8 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1997:69841 CAPLUS
DN 126:94782
TI Vaccine composition containing polyribosylribitol phosphate and method for making same
SO PCT Int. Appl., 21 pp.

CODEN: PIXXD2

IN Arminjon, Francois; Cartier, Jean-Rene

	APPLICATION NO.	DATE
AI	WO 96-FR791	19960524
	FR 95-6417	19950524
	CA 96-2218764	19960524
	AU 96-60086	19960524
	EP 96-917554	19960524
	CN 96-195582	19960524
	NO 97-5366	19971121

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9637222	A1	19961128	WO 96-FR791	19960524
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	FR 2734484	A1	19961129	FR 95-6417	19950524
	FR 2734484	B1	19970627		
	CA 2218764	AA	19961128	CA 96-2218764	19960524
	AU 9660086	A1	19961211	AU 96-60086	19960524
	EP 828511	A1	19980318	EP 96-917554	19960524
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	CN 1190898	A	19980819	CN 96-195582	19960524
	NO 9705366	A	19971121	NO 97-5366	19971121

PY 1996
1996
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1996
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AB A vaccine compn. contg. 1 or more **antigens** comprising the **high** mol. **wt.** capsular polysaccharide of the type b **Haemophilus influenza**, or polyribosylribitol phosphate, coupled to the tetanus toxoid and an aluminum-based adjuvant, wherein the aluminum-based adjuvant has, in its natural state, or following anion addn., a zero point of charge of <7.2. A method for making the vaccine compn. is also described. A vaccine compn. contained aluminum hydroxide 0.25 mg, PRP-T 10 .mu.g, ADP and ATP 1 vaccinating dose each, phosphates 15 .mu.mol, polio **antigen** type I, II, and III 40, 8, and 32 U resp., pertussis toxin 25 .mu.g, buffer 0.125 mL, and water 0.5 mL.

Searcher : Shears 308-4994

L3 ANSWER 9 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1996:606388 CAPLUS
DN 125:245149
TI Synthesis, characterization, and immunologic properties of detoxified lipooligosaccharide from nontypeable **Haemophilus influenzae** conjugated to proteins
SO Infect. Immun. (1996), 64(10), 4047-4053
CODEN: INFIBR; ISSN: 0019-9567
AU Gu, Xin-Xing; Tsai, Chao-Ming; Ueyama, Tomoyo; Barenkamp, Stephen J.; Robbins, John B.; Lim, David J.
PY 1996
AB Nontypeable **Haemophilus influenzae** (**NTHi**) is an important cause of **otitis media** in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a major surface **antigen** of **NTHi** and elicits bactericidal and opsonic antibodies. We prepd. detoxified LOS (dLOS) protein conjugates from **NTHi** for use as exptl. vaccines. LOS from **NTHi** 9274 was treated with anhyd. hydrazine and had its toxicity reduced to clin. acceptable levels. DLOS was bound to tetanus toxoid (TT) or **high-mol.-wt.** proteins (**HMPs**) from **NTHi** through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-**HMP**. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as detd. by double immunodiffusion. S.c. or i.m. injection of the conjugates elicited a 28- to 486-fold rise in the level of IgG antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of IgG antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for **otitis media** and pneumonitis caused by **NTHi**.

L3 ANSWER 10 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1996:455154 CAPLUS
DN 125:139983
TI Identification of surface-exposed B-cell epitopes on **high**-molecular-**weight** adhesion proteins of nontypeable **Haemophilus influenzae**
SO Infect. Immun. (1996), 64(8), 3032-3037
CODEN: INFIBR; ISSN: 0019-9567
AU Barenkamp, Stephen J.; St. Geme, Joseph W., III
PY 1996

AB Two surface-exposed **high**-mol.-**wt**. proteins, HMW1 and HMW2, expressed by a prototypic strain of nontypeable **H**. **influenzae** (**NTHI**) mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to most nontypeable Haemophilus strains. Immunization with an HMW1-HMW2 mixt. modified the course of disease in an animal model of **otitis media**, suggesting the potential usefulness of these proteins as **NTHI** vaccine components. Identification of surface-accessible B-cell epitopes could be important to efforts to develop recombinant or synthetic peptide vaccines based upon these **high**-mol.-**wt**. proteins. The purpose here was to identify surface-accessible epitopes on the HMW1 and HMW2 proteins by using monoclonal antibodies (MAbs) and to det. the prevalence of these epitopes among the **high**-mol.-**wt**. proteins expressed by heterologous nontypeable Haemophilus strains. MAbs were generated by immunizing mice with **high**-mol.-**wt**. proteins purified from prototype strains and were screened by immunoelectron microscopy (IEM) for the ability to recognize surface epitopes. Two MAbs, designated AD6 and 10C5, that recognized surface epitopes by IEM were recovered. To map the epitopes recognized by these 2 MAbs, a set of HMW1 and HMW2 recombinant fusion proteins was constructed using the pGEMEX vectors and the reactivity of the MAbs with these fusion proteins was examd. MAb AD6 recognized an epitope in both HMW1 and HMW2 which mapped to the last 75 amino acids at the C termini of the 2 proteins. When examd. for reactivity with heterologous strains, MAb AD6 recognized **high**-mol.-**wt**. proteins in 75% of 125 unrelated nontypeable Haemophilus strains and, in addn., reacted with 3 of 3 such strains when examd. by IEM. MAb 10C5 recognized an epitope that mapped to a 155-amino-acid segment near the C terminus of HMW1. This epitope was adjacent to but distinct from the AD6 epitope and was absent from HMW2. The 10C5 epitope was expressed by 40% of the AD6 reactive strains. Identification of shared surface-exposed epitopes on the **high**-mol.-**wt**. adhesion proteins suggests the possibility of developing recombinant or synthetic peptide-based vaccines protective against disease caused by the majority of **NTHI** strains.

L3 ANSWER 11 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1996:327952 CAPLUS
DN 125:7851
TI Evaluation of purified UspA from Moraxella catarrhalis as a vaccine in a murine model after active immunization
SO Infect. Immun. (1996), 64(6), 1900-1905
CODEN: INFIBR; ISSN: 0019-9567
AU Chen, Dexiang; McMichael, John C.; VanDerMeid, Karl R.; Hahn, Denise; Mininni, Terri; Cowell, James; Eldridge, John
PY 1996

AB Moraxella catarrhalis causes **otitis media**, laryngitis, and respiratory infections in humans. A **high** -mol.-**wt**. outer membrane protein from this bacterium named ubiquitous surface protein A (UspA) is present on all isolates. A monoclonal antibody (MAb) to UspA that recognizes a conserved epitope of this protein has been shown to promote pulmonary clearance of bacteria in passively immunized. In the present study, M. catarrhalis heterologous isolates were screened by dot blot with a panel of 4 addnl. MAbs specific for surface-exposed epitopes of UspA from M. catarrhalis isolate O35E. Three of the MAbs were specific for O35E, and the 4th reacted with 17 (74%) of the 23 isolates tested. Thus, UspA contains highly conserved, semiconserved, and variable surface-exposed epitopes. The UspA was purified from the O35E isolate by ion-exchange and size-exclusion chromatog., formulated with the adjuvant QS-21, and used to immunize BALB/c mice. Upon pulmonary challenge with either O35E or the heterologous isolate TTA24, significantly fewer bacteria were recovered from the lungs of immunized mice 6 h postchallenge than from control mice. The immune sera from mice or guinea pigs contained high titers of antibodies to the homologous isolate and heterologous isolates in a whole-bacterial-cell ELISA. Sera against UspA, whether prepd. in mice or guinea pigs, had complement-dependent bactericidal activity toward homologous and 11 heterologous M. catarrhalis isolates. These results indicate that the conserved epitopes of the UspA are highly immunogenic and elicit broadly reactive and biol. functional antibodies. UspA may offer protection against M. catarrhalis infections and is being further evaluated as a vaccine candidate.

L3 ANSWER 12 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1996:213484 CAPLUS
DN 124:255432
TI Identification of a second family of **high**-molecular-**weight** adhesion proteins expressed by non-typable **Haemophilus influenzae**
SO Mol. Microbiol. (1996), 19(6), 1215-23
CODEN: MOMIEE; ISSN: 0950-382X
AU Barenkamp, Stephen J.; St. Geme, Joseph W., III
PY 1996
AB We previously reported that two surface-exposed **high**-mol.-**wt**. proteins, HMW1 and HMW2, expressed by a prototypic strain of non-typable **Haemophilus influenzae** (**NTHI**), mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to 70-75% of **NTHI** strains. **NTHI** strains that lack HMW1/HMW2-like proteins remain capable of efficient attachment to cultured human epithelial cells, suggesting the existence of addnl. adhesion mols. We reasoned that characterization of **high**-mol.-**wt**. immunogenic

proteins from an HMW1/HMW2-deficient strain might identify addnl. adhesion proteins. A genomic library was prepd. in .lambda.EMBL3 with chromosomal DNA from non-typable Haemophilus strain 11, a strain that lacks HMW1/HMW2-like proteins. The library was screened immunol. with convalescent serum from a child naturally infected with strain 11, and phage clones expressing **high**-mol.-**wt.** recombinant proteins were identified by Western blot anal. One clone was identified that expressed a protein with an apparent mol. mass greater than 200 kDa. Transformation of non-adherent Escherichia coli strain DH5.alpha. with plasmids contg. the genetic locus encoding this protein gave rise to E. coli transformants that adhered avidly to Chang conjunctival cells. Subcloning and mutagenesis studies localized the DNA conferring the adherence phenotype to a 4.8 kbp fragment, and nucleotide sequence anal. further localized the gene encoding the adhesion protein to a 3.3 kbp open reading frame predicted to encode a protein of 114 kDa. The gene was designated hia for **Haemophilus influenzae adhesin**. Southern anal. revealed an hia homolog in 13 of 15 HMW1/HMW2-deficient non-typable **H. influenzae** strains. In contrast, the hia gene was not present in any of 23 non-typable **H. influenzae** strains which expressed HMW1/HMW2-like proteins. Identification of this second family of **high**-mol.-**wt.** adhesion proteins suggests the possibility of developing vaccines based upon a combination of HMW1/HMW2-like proteins and Hia-like proteins which would be protective against disease caused by most of all non-typable **H. influenzae**.

L3 ANSWER 13 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1996:190693 CAPLUS
DN 124:229356
TI Immunization with **high**-molecular-**weight** adhesion proteins of nontypeable **Haemophilus influenzae** modifies experimental **otitis media** in chinchillas
SO Infect. Immun. (1996), 64(4), 1246-51
CODEN: INFIBR; ISSN: 0019-9567
AU Barenkamp, Stephen J.
PY 1996
AB Prevention of nontypeable **Haemophilus influenzae** **otitis media** by vaccination is an important heath care goal. Proteins important in bacterial adherence deserve consideration as potential vaccine candidates. Two colleagues and I previously identified a family of immunogenic **high**-mol.-**wt.** proteins important in adherence to nontypeable **H**. **influenzae** to human epithelial cells (J. W. St. Geme III, S. Falkow, and S. J. Barenkamp, Proc. Natl. Acad. Sci. USA, 90:2875-2879, 1993). In the work described here, I detd. whether immunization with two such adherence proteins, HMW1 and HMW2,

purified from prototype nontypeable Haemophilus strain 12, would modify the course of exptl. **otitis media** caused by the homologous strain. Chinchillas received three monthly s.c. injections with 40 .mu.g of a HMW1/HMW2 protein mixt. in Freund's adjuvant. One month after the last injection, animals were challenged by intrabullar inoculation with 300 CFU of nontypeable **H. influenzae** 12. Infection developed in five of five control animals vs. 5 of 10 immunized animals (P = 0.08, Fisher exact, one-tailed). Among infected animals, bacterial counts in middle ear fluid specimens 7 days postchallenge were significantly greater in control animals than in immunized animals (P = 0.014, Mann-Whitney U test). Serum antibody titers following immunization were comparable in uninfected and infected animals. However, infection in immunized animals was uniformly assocd. with the appearance of bacteria downregulated in expression of the **high**-mol.-**wt**. proteins, suggesting bacterial selection in response to immunol. pressure. Although protection following immunization was incomplete, these data suggest that the **high**-mol.-**wt**. adhesion proteins are potentially important protective **antigens** which might represent one component of a multicomponent nontypeable Haemophilus vaccine.

L3 ANSWER 14 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1995:1006690 CAPLUS
DN 124:28122
TI Preparation of **antigen** from fermentation broth
SO Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
IN Nishida, Yasukuni

APPLICATION NO.	DATE
JP 94-98059	19940412

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07274993	A2	19951024	JP 94-98059	19940412

PY 1995
AB Fermn. broth of a microorganism is subjected to removal of **high** mol.-**wt**. substances, and used for further culture of the microorganism to prep. **antigen** in the culture supernatant. The method gives high yield and is simple. The **antigen** thus prepd. is useful for induction of antibodies. Prepn. of **antigen** of Streptococcus pyogenes by subjecting the fermn. broth to ultrafiltration to remove the **high** mol.-**wt**. substances was shown.

L3 ANSWER 15 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1995:659115 CAPLUS
DN 123:109185
TI Binding of **Haemophilus influenzae** to purified

mucins from the human respiratory tract
SO Infect. Immun. (1995), 63(7), 2485-92
CODEN: INFIBR; ISSN: 0019-9567
AU Davies, Julia; Carlstedt, Ingemar; Nilsson, Ann-Kristin; Hakansson, Anders; Sabharwal, Hemant; Van Alphen, Loek; Van Ham, Marieke; Svanborg, Catharina
PY 1995
AB Mucins are **high**-mol.-**wt.** glycoproteins and major constituents of the mucus layer which covers the airway surface. The authors have studied the interactions between bacteria, mucins, and epithelial cells from the human respiratory tract. Non-typeable strains of **Haemophilus influenzae** bound purified airway mucins in suspension and on solid phase. Mucins in suspension inhibited the attachment of these strains to nasopharyngeal epithelial cells, while mucin coating of the cells enhanced their binding. In contrast, strains of Streptococcus pneumoniae and encapsulated and other non-typeable **H. influenzae** strains failed to interact with mucins. These **H. influenzae** strains used other strategies for adherence to epithelial cells. The type b strain 770235 attached via fimbriae but also expressed a subcapsular **adhesin** that was detected in a capsule- and fimbria-defective mutant. Mucin pretreatment of these bacteria did not inhibit adherence, but mucin pretreatment of epithelial cells inhibited adherence, probably by shielding of the receptors for these **adhesins**. Non-mucin-binding non-typeable and encapsulated **H. influenzae** strains would, therefore, adhere only after disruption of the mucus layer and exposure of cellular receptors. Differences in tissue toxicity and invasiveness among **H. influenzae** strains may also be influenced by the mucin interactions of the strains.

L3 ANSWER 16 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1994:696730 CAPLUS
DN 121:296730
TI Localization of **high**-molecular-**weight** adhesion proteins of nontypeable **Haemophilus influenzae** by immunoelectron microscopy
SO Infect. Immun. (1994), 62(10), 4460-8
CODEN: INFIBR; ISSN: 0019-9567
AU Bakaletz, L. O.; Barenkamp, S. J.
PY 1994
AB A family of **high-mol.-wt.** (**HMW**) surface-exposed proteins important in the attachment of nontypeable **Haemophilus influenzae** (**NTHi**) to humans epithelial cells was previously identified (J. W. St. Geme III, S. Falkow, and S. J. Barenkamp, Proc. Natl. Acad. Sci. USA 90:2875-2879, 1993). In the present investigation, indirect immunogold labeling and electron microscopy were used to localize

these proteins on three clin. isolates of **NTHi**, mutants deficient in expression of one or both HMW proteins, and embedded sections of human oropharynegeal cells after incubation with **NTHi** strain 12. The filamentous material comprising the proteins was labeled with monoclonal antibodies directed against two prototype HMW proteins (HMW1 and HMW2) of prototype **NTHi** strain 12. Gold labeling was obsd. as a cap or discrete aggregate off one pole or centrally along one long axis of the bacterial cell. Heavily labeled, non-bacterial-cell-assocd., disk-like aggregates of the HMW proteins were frequently noted in both bacterial prepns. as well as in assocn. with the oropharynegeal cell surface and intracellularly. Mutants demonstrated diminished labeling or an absence thereof, resp., which correlated well with their previously demonstrated reduced ability or inability to adhere to Chang conjunctival epithelial cells in vitro. The Haemophilus HMW proteins share antigenic determinants with and demonstrate amino acid sequence similarity to the filamentous hemagglutinin protein of Bordetella pertussis, a crit. **adhesin** of that organism. The studies presented here demonstrate that the Haemophilus proteins and B. pertussis filamentous hemagglutinin show impressive morphol. and perhaps addnl. functional similarity.

L3 ANSWER 17 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1994:576469 CAPLUS
DN 121:176469
TI The HMW1 **adhesin** of nontypeable **Haemophilus influenzae** recognizes sialylated glycoprotein receptors on cultured human epithelial cells
SO Infect. Immun. (1994), 62(9), 3881-9
CODEN: INFIBR; ISSN: 0019-9567
AU St. Geme, Joseph W., III
PY 1994
AB Disease due to nontypeable **H. influenzae** begins with colonization of the upper respiratory tract mucosa. The authors recently reported that two surface-exposed **high** -mol.-**wt**. proteins (HMW1 and HMW2) expressed by a prototypic strain of nonltypeable **H. influenzae** mediate attachment to cultured epithelial cells. In the present study, the authors examd. the nature of the epithelial cells receptor with which HMW1 interacts. Both proteinase K pretreatment and periodate oxidn. of epithelial monolayers resulted in a marked decrease in HMW1-mediated binding, suggesting interaction with a glycoprotein structure. Treatment with peptide-N-glycosidase F produced a similar decrease in attachment and thereby provided further evidence for this conclusion. Desialylation of the epithelial cell surface also reduced binding, implying the presence of sialic acid were capable of inhibiting HMW1-mediated attachment. In summary, these results indicate that the HMW1 **adhesin** interacts with a glycoprotein receptor contg. N-linked

oligosaccharide chains with sialic acid in an .alpha.2-3 configuration.

L3 ANSWER 18 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1994:268066 CAPLUS
DN 120:268066
TI **High**-molecular-**weight** surface-exposed proteins of **Haemophilus influenzae** mediate binding to macrophages
SO J. Infect. Dis. (1994), 169(2), 425-9
CODEN: JIDIAQ; ISSN: 0022-1899
AU Noel, Gary J.; Barenkamp, Stephen J.; St. Geme, Joseph W. III; Haining, W. Nicholas; Mosser, David M.
PY 1994
AB The mol. basis for direct bacteria-macrophage interactions that distinguishes nontypeable (NT) **Haemophilus influenzae** from type b organisms is not known. Because of similarities between filamentous hemagglutinin (FHA) **adhesin** of Bordetella pertussis and **high-mol.-wt**. (**HMW**) proteins commonly expressed by NT **H. influenzae**, the role that **HMW** proteins play in detg. NT **H. influenzae**-macrophage interactions was assessed. In tests with genetically engineered organisms, HMW protein-expressing bacteria bound significantly better than isogenic HMW protein-deficient bacteria to macrophages. HMW protein-dependent binding to macrophages is trypsin-sensitive, is independent of divalent cations, does not occur via the leukocyte integrin CD11b/CD18, and is not affected by galactose-contg. carbohydrates. Organisms bound via HMW proteins remain largely extracellular and viable. Like FHA of Bordetella organisms, HMW proteins mediate binding of NT **H. influenzae** to macrophages. However, unlike the interaction detd. by FHA, this interaction is characteristically one of adhesion and requires addnl. serum opsonization for efficient killing of bacteria by macrophages.

L3 ANSWER 19 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1994:212212 CAPLUS
DN 120:212212
TI Purification and characterization of a **high**-molecular-**weight** outer membrane protein of Moraxella (Branhamella) catarrhalis
SO Infect. Immun. (1994), 62(4), 1150-5
CODEN: INFIBR; ISSN: 0019-9567
AU Klingman, Karin L.; Murphy, Timothy F.
PY 1994
AB Moraxella (Branhamella) catarrhalis is an important bacterial cause of **otitis media** in children and lower respiratory tract infections in adults. The authors describe the

presence of a novel **high-mol.-wt.** outer membrane protein (**HMW**-OMP). This protein varies from 350 to 720 kDa in apparent mol. mass among strains by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The protein was detected on SDS-PAGE in 13 of 14 strains tested. The authors developed a monoclonal antibody and polyclonal antisera to this protein. In immunoblot assays, the protein was present in all 14 strains tested. The immunoblot assays suggest that the protein has at least one epitope that is conserved among strains. A purifn. method using anion-exchange chromatog. is described. Treatment of outer membrane prepns. and purified protein by heat and reducing agents did not change the apparent **mol.** mass of the **HMW**-OMP. Formic acid treatment of outer membrane prepns. and purified **HMW**-OMP produced a single band with an apparent **mol.** mass of 120 to 140 kDa. The authors postulate that this may be the monomer of an oligomeric protein. The **HMW**-OMP, which varies in **mol.** mass among strains and is antigenically conserved, will be studied further to det. its role in the human immune response and may be useful as a marker in studying strain acquisition in patients.

L3 ANSWER 20 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1994:2261 CAPLUS
DN 120:2261
TI Cloning and expression of **high** molecular **weight** surface proteins of non-typeable Haemophilus
SO PCT Int. Appl., 99 pp.
CODEN: PIXXD2
IN Barenkamp, Stephen J.

APPLICATION NO.	DATE
WO 93-US2166	19930316
AU 93-39168	19930316
EP 93-908295	19930316
JP 93-516604	19930316
BR 93-6109	19930316
NO 94-3431	19940915
FI 94-4273	19940915
US 94-302832	19941005
US 95-469880	19950606

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9319090	A1	19930930	WO 93-US2166	19930316
W: AU, BR, CA, FI, JP, KR, NO, RU, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9339168	A1	19931021	AU 93-39168	19930316
AU 669360	B2	19960606		
EP 632814	A1	19950111	EP 93-908295	19930316

Searcher : Shears 308-4994

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

JP 07506248	T2	19950713	JP 93-516604	19930316
BR 9306109	A	19971118	BR 93-6109	19930316
NO 9403431	A	19941110	NO 94-3431	19940915
FI 9404273	A	19941115	FI 94-4273	19940915
US 5603938	A	19970218	US 94-302832	19941005
US 5876733	A	19990302	US 95-469880	19950606

PY 1993
1993
1996
1995
1995
1997
1994
1994
1997
1999

AB The genes for **high** mol. **wt.** surface proteins HMW1 and 2 of **H. influenzae** are cloned and sequenced. The amino acid sequences of HMW1 and 2 derived from the genes had high homol. with that of the filamentous hemagglutinin of Bordetella pertussia. The HMW1 and 2 are useful for prepn. of protective **antigens** against nontypeable Haemophilus-assocd. diseases such as otitis, sinusitis, bronchitis, etc., and as carrier for the protective Hib carrier polysaccharides in a conjugate vaccine against meningitis. The genes for the **high** mol. **wt.** surface proteins were cloned from a genomic library of **H. influenzae** constructed on .lambda.EMBL3 by immunol. screening using an human antibody against the **high** mol. **wt.** surface proteins. Also shown was the adherence of the HMW1 and 2 on the Chang epithelial cells. HMW3 and 4 were also cloned and partially sequenced.

L3 ANSWER 21 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1993:206310 CAPLUS
DN 118:206310
TI Cloning, expression, and DNA sequence analysis of genes encoding nontypeable **Haemophilus influenzae high** -molecular-**weight** surface-exposed proteins related to filamentous hemagglutinin in Bordetella pertussis
SO Infect. Immun. (1992), 60(4), 1302-13
CODEN: INFIBR; ISSN: 0019-9567
AU Barenkamp, Stephen J.; Leininger, Elizabeth
PY 1992
AB A group of **high**-mol.-**wt.** surface-exposed proteins of nontypeable **H. influenzae** are major targets of human serum antibody. To further characterize these proteins, genes encoding 2 related **high**-mol.-**wt.**

proteins were cloned and sequenced from a prototype nontypeable Haemophilus strain. The gene encoding a 120-kDa Haemophilus protein consisted of a 4.4-kbp open reading frame, and the gene encoding a 125-kDa protein consisted of a 4.6-kbp open reading frame. The first 1259 bp of the 2 genes were identical. Thereafter, the sequences began to diverge, but overall they were 80% identical, and the derived amino acid sequences showed 70% identity. A protein sequence homol. search demonstrated similarity between the derived amino acid sequences of both cloned genes and the derived amino acid sequence of the gene encoding filamentous hemagglutinin, a surface protein produced by the gram-neg. pathogen B. pertussis. Antiserum raised against a recombinant protein encoded by the 4.6-kbp open reading frame recognized both the 120- and the 125-kDa proteins in the prototype strain as well as antigenically related **high** -mol.-**wt.** proteins in 75% of a collection of 125 epidemiol. unrelated nontypeable **H. influenzae** strains. The antiserum directed against the recombinant protein also recognized purified filamentous hemagglutinin. A murine monoclonal antibody to filamentous hemagglutinin recognized both the 120-kDa and the 125-kDa protein in the prototype strain as well as proteins identical to those recognized by the recombinant-protein antiserum in 35% of the nontypeable **H. influenzae** strain collection. Thus, the authors have identified and partially characterized a group of highly immunogenic surface-exposed proteins of nontypeable **H. influenzae** which are related to the filamentous hemagglutinin of B. pertussis.

L3 ANSWER 22 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1990:495780 CAPLUS
DN 113:95780
TI Expression in Escherichia coli of a **high**-molecular-**weight** protective surface **antigen** found in nontypeable and type b **Haemophilus influenzae**
SO Infect. Immun. (1990), 58(6), 1909-13
CODEN: INFIBR; ISSN: 0019-9567
AU Thomas, W. R.; Callow, M. G.; Dilworth, R. J.; Audesho, A. A.
PY 1990
AB An E. coli clone producing a **high**-mol.-**wt.** surface **antigen** of **H. influenza** type b (Hib) was isolated from a library of Hib DNA fragments cloned as lysogens in a lambda replacement vector. The **antigen** is found in sarcosyl-insol. outer membrane protein prepns. and was produced by all 36 **H. influenza** isolates tested. Absorption studies indicated that the **antigen** is a surface determinant on all isolates tested. Antibodies to the **antigen** (D15) were found in 8 of 9 convalescent-phase sera from children with invasive Hib infection. Affinity-purified antibodies prepd. against the cloned **antigen** gave protection against the development of bacteremia in a rat pup model.

Searcher : Shears 308-4994

L3 ANSWER 23 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1987:573808 CAPLUS
DN 107:173808
TI **Haemophilus influenzae** type b lipooligosaccharide: stability of expression and association with virulence
SO Infect. Immun. (1987), 55(9), 1979-86
CODEN: INFIBR; ISSN: 0019-9567
AU Kimura, Alan; Patrick, Christian C.; Miller, Elizabeth E.; Cope, Leslie D.; McCracken, George H., Jr.; Hansen, Eric J.
PY 1987
AB Spontaneous antigenic and phenotypic variations in the lipooligosaccharide (LOS) of 2 strains of **H. influenzae** type b (Hib) were previously shown to be assocd. with changes in virulence (A. Kimura and E. J. Hansen, 1986). The goal of the present study was to define further the stability of LOS expression by this pathogen and the role of Hib LOS in virulence. Variation in LOS antigenic reactivity, as detected with LOS-specific-monoclonal antibodies, was obsd. in 3 of 30 Hib strains after single-colony passage. When large nos. of individual colonies from 7 other Hib strains were screened, however, spontaneous LOS antigenic variation was detected in all of the strains. Antigenic variation was not consistently assocd. with an altered LOS phenotype, as detd. by SDS-PAGE and Ag staining of LOS prepns. Changes in the LOS antigenic phenotype were correlated with altered virulence potential in 2 strains. In these strains, acquisition of reactivity with certain LOS-directed monoclonal antibodies was assocd. with the synthesis of a higher-mol.-wt. LOS, enhanced virulence, and increased resistance to serum killing involving the classical complement pathway.

L3 ANSWER 24 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1985:404697 CAPLUS
DN 103:4697
TI Composition and antigenic activity of the oligosaccharide moiety of **Haemophilus influenzae** type b lipooligosaccharide
SO Infect. Immun. (1985), 48(2), 324-30
CODEN: INFIBR; ISSN: 0019-9567
AU Inzana, Thomas J.; Seifert, William E., Jr.; Williams, Robert P.
PY 1985
AB The oligosaccharide moiety of the lipooligosaccharide of **H. influenzae** type b strain Eag was isolated from the lipid component by mild acid hydrolysis and purified by gel filtration. Fast atom bombardment-mass spectrometry indicated that the lipid-free oligosaccharide had a basic mol. wt. of 1768; polysaccharides comparable to **high**-mol.-**wt.** O side chains were not found. Glucose, galactose, galactosamine, heptose, 3-deoxy-D-manno-2-octulosonic acid (KDO), ethanolamine, and

phosphate were identified in the lipid-free oligosaccharide by colorimetric assays, gas chromatog.-mass spectrometry, or amino acid anal. The presence of KDO was not clearly established by a thiobarbituric acid assay or by growth inhibition by a diazaborine deriv. thought to block KDO synthesis. However, the semicarbizide assay and gas chromatog.-mass spectrometry confirmed the presence of KDO. Lectin pptn. by Eag lipooligosaccharide in gels indicated that .beta.-D-galactose was present and that some of this monosaccharide was a terminal, nonreducing residue linked to N-acetyl-D-galactosamine. The lipid-free oligosaccharide was antigenic and completely inhibited lipooligosaccharide antibody (predominantly IgG and IgM) in an enzyme-linked immunosorbent assay, whereas the solubilized lipid A moiety did not. **H. influenzae** Type b lipid-free oligosaccharide differed from core oligosaccharide of Salmonella lipooligosaccharide by the presence of galactosamine and a smaller percentage of heptose and KDO.

L3 ANSWER 25 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1985:94049 CAPLUS
DN 102:94049
TI A minor **high**-molecular-**weight** outer membrane protein of **Haemophilus influenzae** type b is a protective **antigen**
SO Infect. Immun. (1985), 47(1), 253-9
CODEN: INFIBR; ISSN: 0019-9567
AU Kimura, Alan; Gulig, Paul A.; McCracken, George H., Jr.; Loftus, Theresa A.; Hansen, Eric J.
PY 1985
AB Cell surface-exposed antigenic determinants of several **high** -mol.-**wt.** outer membrane proteins of **H. influenzae** type b (Hib) have been shown to be consistently immunogenic in human infants convalescing from Hib meningitis. A monoclonal antibody (mab), 6G12, directed against one of these cell surface-exposed outer membrane proteins that has an apparent mol. wt. of 98,000 (98K) was identified by radioimmunopptn. anal. Of 120 clin. isolates of Hib, 83 were found to possess antigenic determinants which reacted with mab 6G12 in a colony blot-radioimmunoassay procedure, indicating that the antigenic determinant recognized by mab 6G12 is present in the majority of Hib strains. A different radioimmunoassay, which uses whole Hib cells as **antigen**, confirmed that strains reactive with mab 6G12 in the colony blot-radioimmunoassay procedure possessed a cell surface-exposed and antibody-accessible antigenic determinant recognized by this mab. Hib strains which did not react with mab 6G12 were found to lack a 98K protein. Passive immunization with mab 6G12 reduced the level of bacteremia that developed in infant rats challenged with the homologous Hib strain against which this mab was raised. In contrast, no protection was obsd. when the challenge strain was one which lacks the antigenic determinant

recognized by mab 6G12. Radioimmunopptn. anal. of sera from human infants convalescing from Hib meningitis detected an antibody response directed against the 98K protein. The protection against exptl. Hib disease provided by antibody to the 98K protein, the immunogenicity of this protein in human infants, and its presence in a majority of Hib strains indicate that the 98K outer membrane protein may have potential for vaccine development.

L3 ANSWER 26 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1983:140177 CAPLUS
DN 98:140177
TI Structural studies of the **Haemophilus influenzae** capsular polysaccharides
SO Haemophilus Influenzae: Epidemiol., Immunol., Prev. Dis., [Pap. Conf.] (1982), Meeting Date 1981, 185-96. Editor(s): Sell, Sarah Hamilton; Wright, Peter F. Publisher: Elsevier, New York, N. Y. CODEN: 49GIAZ
AU Egan, William M.; Tsui, Fai Po; Zon, Gerald
PY 1982
AB The structures of the repeating units of the 6 **H. influenzae** serotype capsular polysaccharides (a-f) were detd. by a combination of chem. and NMR spectroscopic techniques. Four of the capsular polysaccharides were phosphate esters. All 6 polysaccharides were **high**-mol.-**wt.** polymers composed of acidic disaccharide repeat units; types a, b, c, and f were acidic as a result of phosphoric diester groups, and types d and e were acidic as a result of carboxylic acid groups. Types d and e contained the unusual capsular constituent, 2-acetamido-2-deoxy-D-mannose uronic acid.

L3 ANSWER 27 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1978:421972 CAPLUS
DN 89:21972
TI Purification of specific precipitinogen and extraction of endotoxin from **Haemophilus influenzae**
SO J. Clin. Pathol. (1978), 31(4), 370-7
CODEN: JCPAAK; ISSN: 0021-9746
AU Van der Zwan, J. C.; Dankert, J.; De Vries, K.; Orie, N. G. M.; Kauffman, H. F.
PY 1978
AB After purifying a **H. influenzae** precipitinogen from endotoxic activity by means of ultracentrifugation, column chromatog. (Sepharose 6B), and ion exchange chromatog. (DEAE Sephadex A25) a fraction was obtained which still contained a specific precipitinogen that was virtually free of endotoxin. Furthermore, during the chromatog. procedures fractions with a high and a low mol. wt. endotoxic activity were found. The limulus lysate test was more sensitive in the **high** mol. **wt**. fractions and the LD50 in mice in the low mol. wt. fractions with

endotoxic activity.

L3 ANSWER 28 OF 28 CAPLUS COPYRIGHT 1999 ACS
AN 1978:168285 CAPLUS
DN 88:168285
TI Immunogenicity in weanling rabbits of a polyribophosphate complex from **Haemophilus influenzae** type b
SO J. Infect. Dis. (1977), 136(Suppl.), 63-70
CODEN: JIDIAQ; ISSN: 0022-1899
AU Anderson, Porter; Smith, David H.
PY 1977
AB Polyribophosphate (PRP), the capsular polysaccharide of **H. influenzae** type b, is more effectively immunogeic when it is assocd. with the bacterium than when it is in the purified form that is being tested as a vaccine for humans. To analyze this difference, there was isolated from **H. influenzae** type b a **high**-mol.-**wt.**, sol. complex, in which PRP appears to be combined with protein (.apprx.7% protein). The pyrogenicity and limulus lysate gelation activity of the complex suggest that a small amt. of lipopolysaccharide also is present. The protein was resolved into 5 polypeptides by electrophoresis in polyacrylamide gel contg. Na dodecyl sulfate. In weanling rabbits, which do not respond to purified PRP, the complex induces high titers of antibody to PRP, in an anamnestic pattern. Bactericidal antibody to other bacterial components was also elicited. Equil. d. gradient centrifugation of the complex indicated that most of th immunogenicity of PRP resides in the least dense fractions, which are high in protein, low in polysaccharide, and active in the limulus lysate test; denser fractions that react strongly with limulus lysate but are poor in protein were much less immunogenic.

FILE 'CAPLUS' ENTERED AT 12:34:40 ON 25 MAR 1999
L4 55 SEA ABB=ON PLU=ON L1 AND ((HMW# OR HMP#)(S)MOLECUL? OR HIGH(1W)(WEIGHT OR WT))
L5 28 SEA ABB=ON PLU=ON L4 AND (ANTIGEN OR ADHESIN OR HNI47 OR HNI 47 OR HSP OR HEAT(W)SHOCK)
L6 0 SEA ABB=ON PLU=ON L5 NOT L3

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB, DRUGLAUNCH' ENTERED AT 12:36:14 ON 25 MAR 1999)
L7 126 S L5
L8 58 DUP REM L7 (68 DUPLICATES REMOVED)

DUPLICATE 1

L8 ANSWER 1 OF 58 MEDLINE
AN 1999081722 MEDLINE
DN 99081722
TI Characterization of emb, a gene encoding the major **adhesin** of Streptococcus defectivus.

AU Manganelli R; van de Rijn I
CS Department of Microbiology and Immunology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.
NC AI37320 (NIAID)
CA12107 (NCI)
SO INFECTION AND IMMUNITY, (1999 Jan) 67 (1) 50-6.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-AF067776
EM 199903
EW 19990305
AB Streptococcus defectivus is one of the nutritionally variant streptococci, a class of viridans group streptococci first isolated from patients with endocarditis and **otitis media** . In previous studies, NVS-47, a clinical isolate of S. defectivus, was shown to bind to the extracellular matrix. A **high** -molecular-**weight** surface protein was identified and proposed to be responsible for mediating this binding. In the present study, the gene encoding this protein was identified by transposon mutagenesis and characterized. The gene (emb) was found to be larger than 14 kb and was partially sequenced. It encodes a protein containing at least 50 repeats of 77 amino acids predicted to assume an alternating coiled-coil conformation. The domain responsible for extracellular matrix binding was mapped to the N terminus of the protein. From sequence analysis, Emb is proposed to be the prototype of a new family of streptococcal fibrillar proteins.

L8 ANSWER 2 OF 58 MEDLINE DUPLICATE 2
AN 1998234022 MEDLINE
DN 98234022
TI Nasopharyngeal colonization with nontypeable **Haemophilus influenzae** in chinchillas.
AU Yang Y P; Loosmore S M; Underdown B J; Klein M H
CS Research Center, Pasteur Merieux Connaught Canada, North York, Ontario.. ypyang@ca.pmc-vacc.com
SO INFECTION AND IMMUNITY, (1998 May) 66 (5) 1973-80.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199807
EW 19980703
AB Colonization of the nasopharynx by a middle ear pathogen is the first step in the development of **otitis media** in

humans. The establishment of an animal model of nasopharyngeal colonization would therefore be of great utility in assessing the potential protective ability of candidate vaccine **antigens** (especially **adhesins**) against **otitis media**. A chinchilla nasopharyngeal colonization model for nontypeable **Haemophilus influenzae** (**NTHI**) was developed with antibiotic-resistant strains. This model does not require coinfection with a virus. There was no significant difference in the efficiency of **NTHI** colonization between adult (1- to 2-year-old) and young (2- to 3-month-old) animals. However, the incidence of middle ear infection following nasopharyngeal colonization was significantly higher in young animals (83 to 89%) than in adult chinchillas (10 to 30%). Chinchillas that had recovered either from a previous middle ear infection caused by **NTHI** or from an infection by intranasal inoculation with **NTHI** were completely protected against nasopharyngeal colonization with a homologous strain and were found to be the best positive controls in protection studies. Systemic immunization of chinchillas with inactivated whole-cell preparations significantly protected animals not only against homologous **NTHI** colonization but also partially against heterologous **NTHI** infection. In all protected animals, significant serum anti-P6 and anti-**HMW** antibody responses were observed. The outer membrane P6 and **high-molecular-weight** (**HMW**) proteins appear to be promising candidate vaccine **antigens** to prevent nasopharyngeal colonization and middle ear infection caused by **NTHI**.

DUPLICATE 3

L8 ANSWER 3 OF 58 MEDLINE
AN 1998234010 MEDLINE
DN 98234010
TI Synthesis and characterization of lipooligosaccharide-based conjugates as vaccine candidates for Moraxella (Branhamella) catarrhalis.
AU Gu X X; Chen J; Barenkamp S J; Robbins J B; Tsai C M; Lim D J; Battey J
CS Laboratory of Immunology, National Institute on Deafness and Other Communication Disorders, Rockville, Maryland 20850, USA.. xgu@pop.nidcd.nih.gov
SO INFECTION AND IMMUNITY, (1998 May) 66 (5) 1891-7.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199807
EW 19980703
AB Moraxella (Branhamella) catarrhalis is an important cause of

otitis media and sinusitis in children and of lower respiratory tract infections in adults. Lipooligosaccharide (LOS) is a major surface **antigen** of the bacterium and elicits bactericidal antibodies. Treatment of the LOS from strain ATCC 25238 with anhydrous hydrazine reduced its toxicity 20,000-fold, as assayed in the Limulus amebocyte lysate (LAL) test. The detoxified LOS (dLOS) was coupled to tetanus toxoid (TT) or **high-molecular-weight** proteins (**HMP**) from nontypeable **Haemophilus influenzae** through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-**HMP**. The molar ratios of dLOS to TT and **HMP** conjugates were 19:1 and 31:1, respectively. The antigenicity of the two conjugates was similar to that of the LOS, as determined by double immunodiffusion. Subcutaneous or intramuscular injection of both conjugates elicited a 50- to 100-fold rise in the geometric mean of immunoglobulin G (IgG) to the homologous LOS in mice after three injections and a 350- to 700-fold rise of anti-LOS IgG in rabbits after two injections. The immunogenicity of the conjugate was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced antisera had complement-mediated bactericidal activity against the homologous strain and heterologous strains of M. catarrhalis. These results indicate that a detoxified LOS-protein conjugate is a candidate for immunization against M. catarrhalis diseases.

L8 ANSWER 4 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 4
AN 1999:111775 BIOSIS
DN PREV199900111775
TI A putative **adhesin** gene cloned from Campylobacter jejuni.
AU Kelle, K.; Pages, J.-M.; Bolla, J.-M. (1)
CS (1) CJF 96-06, EA 2197, Faculte Med. Timone, 27 boulevard Jean Moulin, 13385 Marseille Cedex 05 France
SO Research in Microbiology, (Nov.-Dec., 1998) Vol. 149, No. 10, pp. 723-733.
ISSN: 0923-2508.
DT Article
LA English
SL English; French
AB Thirteen Campylobacter jejuni strains of human origin showed differing behaviours when analysed for their ability to bind the Caco-2 cell line in vitro, suggesting variations in genetic complements and/or regulation. We designed an oligonucleotide probe corresponding to a highly conserved part of **adhesins** from various Gram-negative bacteria. Among our laboratory collection, Southern hybridization has demonstrated that only a discrete number of strains harbour this sequence. The corresponding gene has been cloned from our prototype strain and sequence analysis has confirmed homology with Gram-negative bacterial **adhesins**. The ORF

corresponded to 869 amino acids; we named this protein P95. Protein sequence similarity assessment demonstrated that this gene product belongs to the family of proteins including the filamentous haemagglutinin of Bordetella pertussis and the **high -molecular-weight** surface-exposed **adhesins** of **Haemophilus influenzae**. Comparison of adhesion and hybridization results emphasized the involvement of this gene in an essential pathogenic process of Campylobacter.

DUPLICATE 5

L8 ANSWER 5 OF 58 MEDLINE
AN 1998084498 MEDLINE
DN 98084498
TI Prevalence and distribution of the hmw and hia genes and the HMW and Hia **adhesins** among genetically diverse strains of nontypeable **Haemophilus influenzae**.
AU St. Geme J W 3rd; Kumar V V; Cutter D; Barenkamp S J
CS Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, and St. Louis Children's Hospital, Missouri 63110, USA.. stgeme@borcim.wustl.edu
NC 1RO1 DC-02873-01 (NIDCD)
SO INFECTION AND IMMUNITY, (1998 Jan) 66 (1) 364-8.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199803
AB Nontypeable **Haemophilus influenzae** is a common cause of human disease and initiates infection by colonizing the upper respiratory tract. In previous work we identified **high -molecular-weight adhesins** referred to as **HMW1** and **HMW2**, expressed by nontypeable strain 12, and determined that most strains of nontypeable **H . influenzae** express one or two antigenically related proteins. More recently, we determined that some strains lack **HMW1**- and **HMW2**-like proteins and instead express an **adhesin** called Hia. In the present study, we determined the prevalence and distribution of the **hmw** and hia genes in a collection of 59 nontypeable strains previously characterized in terms of genetic relatedness. Based on Southern analysis, 47 strains contained sequences homologous to the **hmw1** and **hmw2** genes and nine strains contained homologs to hia. No strain harbored both **hmw** and hia, and three strains harbored neither. Although the **hmw** and hia genes failed to define distinct genetic divisions, the **hmw**-deficient strains formed small clusters or lineages within the larger population structure. Additional analysis established that the IS1016 insertion element was uniformly absent from strains containing **hmw** sequences but was present in two-thirds of

the **hmw**-deficient strains. As IS1016 is associated with the capsule locus (cap) in most encapsulated strains of **H. influenzae**, we speculate that **hmw**-deficient nontypeable strains evolved more recently from an encapsulated ancestor.

L8 ANSWER 6 OF 58 MEDLINE
AN 1998239408 MEDLINE
DN 98239408
TI Heterogeneity in the protein cores of mucins isolated from human middle ear effusions: evidence for expression of different mucin gene products.
AU Hutton D A; Fogg F J; Kubba H; Birchall J P; Pearson J P.
CS Department of Physiological Sciences, University of Newcastle Upon Tyne, UK.
SO GLYCOCONJUGATE JOURNAL, (1998 Mar) 15 (3) 283-91.
Journal code: BJJ. ISSN: 0282-0080.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
EW 19980904
AB **High** molecular **weight** mucins were isolated and purified from human middle ear effusions of children with **Otitis Media** with Effusion (OME) classified into three groups, (1) thick and (2) thin from anatomically normal children and (3) effusions from cleft palate patients. Amino acid analyses of the purified mucins from the three pools were similar but not identical with characteristic contents of serine threonine and proline (32%, 28%, and 38% for pools (1) (2) and (3) respectively). Proteinase resistant glycopeptide fragments corresponding to the tandem repeat domains of cloned mucin genes showed marked differences both between the three mucin pools and with the composition of the tandem repeat sequences of the cloned mucin genes expressed in the airways. Studies on the antigenic identity of middle ear mucins found an epitope likely to be present on MUC5AC, but only accounting for a maximum of 15% by weight and no reactivity was found with antibodies to MUC2 or MUC1. A polyclonal antibody raised to thick effusion mucins reacted strongly with human salivary mucin suggesting the presence of MUC5B epitopes. These studies suggest that more than one mucin gene product is secreted by the human middle ear mucosa and that there may be further mucin genes expressed by the middle ear that have yet to be cloned.

L8 ANSWER 7 OF 58 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 1998:98321 SCISEARCH
GA The Genuine Article (R) Number: YT330
TI Outer-membrane **antigen** expression by Moraxella

(Branhamella) catarrhalis influences pulmonary clearance

AU Kyd J M; Cripps A W; Murphy T F (Reprint)

CS UNIV CANBERRA, FAC SCI APPL, BELCONNEN, ACT 2616, AUSTRALIA (Reprint); UNIV CANBERRA, FAC SCI APPL, BELCONNEN, ACT 2616, AUSTRALIA; SUNY BUFFALO, DEPT MED, DIV INFECT DIS, BUFFALO, NY 14260; SUNY BUFFALO, DEPT MICROBIOL, BUFFALO, NY 14260

CYA AUSTRALIA; USA

SO JOURNAL OF MEDICAL MICROBIOLOGY, (FEB 1998) Vol. 47, No. 2, pp. 159-168.
Publisher: CHAPMAN HALL LTD, 2-6 BOUNDARY ROW, LONDON, ENGLAND SE1 8HN.
ISSN: 0022-2615.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 21

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Moraxella (Branhamella) catarrhalis is a common respiratory tract pathogen in man. The bacterium shows a strong tendency to form aggregates in vitro. A variant strain of M. catarrhalis that showed a reduced tendency to form aggregates was selected by successive in-vitro passage in broth culture from which aggregates had settled. The non-clumping variant strain showed alteration in expression of outer-membrane **antigens**, including the **HMW**-OMP, an outer-membrane protein of c. 200 kDa, outer-membrane protein CD and lipo-oligosaccharide. A mouse model for pulmonary challenge with M. catarrhalis revealed significant differences in the rate of clearance of the isogenic variant strains from the lung. The parent strain caused enhanced recruitment of neutrophils to the lung and more rapid clearance of bacteria from the lungs in comparison to the non-clumping variant. It is concluded that alteration of expression of surface **molecules** by M. catarrhalis has a significant impact in an in-vivo model of pulmonary clearance.

L8 ANSWER 8 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 97-13226 BIOTECHDS

TI **High** mol.**wt**. proteins of non-typeable **Haemophilus influenzae**; vector expression in host cell for recombinant protein production and application in vaccine production

AU Barenkamp S J

PA Barenkamp S J

LO Webster Grove, MO, USA.

PI WO 9736914 9 Oct 1997

AI WO 97-US4707 1 Apr 1997

PRAI US 96-617697 1 Apr 1996

DT Patent

LA English

OS WPI: 97-503038 [46]

Searcher : Shears 308-4994

AN 97-13226 BIOTECHDS
AB The following are claimed: isolated and purified DNAs encoding **high** mol.**wt**. proteins HMW3 and HMW4 of a non-typeable Haemophilus sp., having defined DNA sequences of 4,794 and 4,803 bp and encode proteins with 1,599 and 1,600 amino acids; a vector containing the DNA for transformation of a host; an isolated and purified **high** mol.**wt**. protein retaining the immunological ability to protect against disease caused by a non-typeable Haemophilus sp., characterized by at least one surface-exposed B-lymphocyte epitope that is recognized by monoclonal antibody AD6; a conjugate containing the protein linked to an **antigen**, hapten or polysaccharide for eliciting an immune response to the **antigen**, hapten or polysaccharide; a synthetic peptide having a protein sequence containing 6-150 amino acids and corresponding to at least one protective epitope of the HMW1 (125 kD, 5,116 bp, 1,536 amino acids), HMW2 (120 kD, 4,937 bp, 1,477 amino acids), HMW3 (125 kD) or HMW4 (123 kD) protein, where the protein is recognized by AD6 and/or 10C5. The proteins and peptides can be used in vaccines against **Haemophilus influenzae** infection. (183pp)

L8 ANSWER 9 OF 58 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 97:809230 SCISEARCH
GA The Genuine Article (R) Number: YD176
TI A protective epitope of Moraxella catarrhalis is encoded by two different genes
AU Aebi C; Maciver I; Latimer J L; Cope L D; Stevens M K; Thomas S E; McCracken G H; Hansen E J (Reprint)
CS UNIV TEXAS, SW MED CTR, DEPT MICROBIOL, HAMON BLDG, NA6-200, 6000 HARRY HINES BLVD, DALLAS, TX 75235 (Reprint); UNIV TEXAS, SW MED CTR, DEPT MICROBIOL, DALLAS, TX 75235; UNIV TEXAS, SW MED CTR, DEPT PEDIAT, DALLAS, TX 75235
CYA USA
SO INFECTION AND IMMUNITY, (NOV 1997) Vol. 65, No. 11, pp. 4367-4377. Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0019-9567.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 70
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The **high**-molecular-**weight** UspA protein of Moraxella catarrhalis has been described as being both present on the surface of all M. catarrhalis disease isolates examined to date and a target for a monoclonal antibody (MAI, 17C7) which enhanced pulmonary clearance of this organism in a mouse model system (M. E. Helminen ct al., J. Infect. Dis. 170:867-872, 1994). A recombinant bacteriophage that formed plaques which bound MAb 17C7 was shown to

contain a M. catarrhalis gene, designated uspA1, that encoded a protein with a calculated molecular weight of 88,271. Characterization of an isogenic uspA1 mutant revealed that elimination of expression of UspA1 did not eliminate the reactivity of M. catarrhalis with MAb 17C7. In addition, N-terminal amino acid analysis of internal peptides derived from native UspA protein and Southern blot analysis of M. catarrhalis chromosomal DNA suggested the existence of a second UspA-like protein. A combination of epitope mapping and ligation-based PCR methods identified a second M. catarrhalis gene, designated uspA2, which also encoded the MAb 17C7-reactive epitope. The UspA2 protein had a calculated molecular weight of 62,483. Both the isogenic uspA1 mutant and an isogenic uspA1 mutant possessed the ability to express a very-**high** -molecular-**weight antigen** that bound MAb 17C7. Southern blot analysis indicated that disease isolates of M. catarrhalis likely possess both uspA2 and uspA2 genes. Both UspA1 and UspA2 most closely resembled **adhesins** produced by other bacterial pathogens.

L8 ANSWER 10 OF 58 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-24625 DRUGU M T
TI Vaccination against middle-ear bacterial and viral pathogens.
AU Giebink G S
CS Univ.Minnesota
LO Minneapolis, Minn., USA
SO Ann.N.Y.Acad.Sci. (830, 330-52, 1997) 3 Tab. 121 Ref.
CODEN: ANYAA9 ISSN: 0077-8923
AV Box 296 May, 420 Delaware Street, S.E., Minneapolis, MN 55455, U.S.A. (e-mail: giebi001@maroon.tc.umn.edu).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 98-24625 DRUGU M T
AB Vaccination against middle-ear bacterial and viral pathogens is reviewed with reference to pneumococcal vaccines, conjugate pneumococcal vaccines, **Haemophilus influenzae** vaccines (nontypable), Moraxella catarrhalis vaccines, respiratory viral vaccines (including influenza vaccine) and passive immunoprophylaxis. **Otitis media** can be prevented by systemic immunization. Passive immunoprophylaxis also has potential for preventing this disease.
ABEX **Otitis media** can be prevented by systemic immunization. Pneumococcal conjugate vaccines are being developed to circumvent T-independence of these **antigens** and provide durable immunity at a very young age.Several pneumococcal conjugate vaccines are being tested clinically. Potential vaccine **antigens** of nontypable **H. influenzae** include outer membrane proteins, pili, fimbriae and **high**

molecular **weight** proteins. Several outer membrane proteins show extensive homology among strains, but the surface determinants of others are very variable so that antibodies to surface epitopes of one strain will not bind to surface epitopes of another. Several M. catarrhalis outer membrane proteins and **high** molecular **weight** protein **antigens** have vaccine potential, but no functional correlates of protection have been identified. There is no evidence to suggest that antibodies to M. catarrhalis protect against **otitis media**. Attenuated viral vaccines may prevent childhood **otitis media**. 2 Clinical trials with killed influenza vaccines have shown a reduction in **otitis media** among vaccine recipients compared to controls during periods of high influenza disease activity in the community. Passive immunoprophylaxis may also prevent **otitis media**. Human bacterial polysaccharide immune globulin protects against pneumococcal **otitis media** in children and in a chinchilla model of **otitis media**. High-dose RSV-enriched Ig reduces the incidence and severity of RSV lower respiratory tract infection in high risk children. Passive immunoprophylaxis may also be effective in children with specific immune deficiencies and in patients who fail to respond to vaccines. (E83)

L8 ANSWER 11 OF 58 TOXLINE
AN 1997:60389 TOXLINE
DN CRISP-97-C00019-02
TI VACCINE DEVELOPMENT OF NONTYPEABLE **HAEMOPHILUS INFLUENZAE**.
AU GU X
CS NIDCD, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NAT'L. INST. ON DEAFNESS & OTHER COMMUNICATION DISORDERS.
NC Z01DC00019-02
SO (1996). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
DT (RESEARCH)
FS CRISP
LA English
EM 199705
AB RPROJ/CRISP Nontypeable **Haemophilus influenzae** (**NTHi**) is an important cause of **otitis media** in children and of pneumonitis in adults with depressed resistance. There is no vaccine available for **NTHi**. Lipooligosaccharide (LOS) is a major surface **antigen** of **NTHi** and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from **NTHi** for use as an experimental vaccine.

Searcher : Shears 308-4994

LOS from strain 9274 was treated with anhydrous hydrazine and its toxicity was reduced to clinically acceptable levels. dLOS was bound to tetanus toxoid or **high** molecular **weight** proteins from **NTHi** through a linker to form conjugates. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion or ELISA. Subcutaneous or intramuscular injection of the conjugates elicited a 28 to 486-fold rise of IgG antibodies in mice to the homologous LOS after 2 to 3 injections, and a 169 to 243-fold rise in rabbits after 2 injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and the heterologous strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for **otitis media** and pneumonitis caused by **NTHi**.

L8 ANSWER 12 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 96-14067 BIOTECHDS
TI Nucleic acid containing a promoter and a gene encoding a non-Bordetella gene product;
an expression system for cholera toxin or **Haemophilus influenzae high** mo.**wt**. outer membrane protein **antigen** expression in Bordetella pertussis
AU Loosmore S M; Yacoob R K; Zealey G R; Klein M H
PA Connaught-Lab.
LO Willowdale, Ontario, Canada.
PI WO 9626282 29 Aug 1996
AI WO 96-CA107 23 Feb 1996
PRAI US 95-393334 23 Feb 1995
DT Patent
LA English
OS WPI: 96-425088 [42]
AN 96-14067 BIOTECHDS
AB A nucleic acid, of a specified DNA sequence, containing a promoter and a signal peptide functional in Bordetella and operatively coupled to a heterologous gene encoding a non-Bordetella gene product, where the gene is transcriptionally regulated by the promoter, is claimed. Also claimed are: a plasmid adapted for transformation of Bordetella containing the nucleic acid; and a recombinant Bordetella strain containing the nucleic acid optionally integrated into its genome, and which secretes the gene product. The gene product is an enzyme, **antigen**, immunogen, allergen, enzyme-inhibitor, hormone, lymphokine, immunoglobulin or fragment, toxin or subunit, mammalian protein, structural protein or receptor, preferably a cholera toxin B subunit. The **antigen** is a **high** mol.**wt**

. outer membrane protein of a non-typable **Haemophilus influenzae** strain, preferably HMW1 or HMW2 protein. The plasmid is DS-546-1, JB-898-2-1, DS-729-1-1, DS-729-2-1, JB-1201-4, JB-1141-5, JB-1957-27, JB-1989-R-1, DS-1719-28 and DS-1732R-14, and the transformed bacterium is B. pertussis, B. parapertussis, B. bronchiseptica or B. avium, preferably B. pertussis 694-46 (ATCC 55,654). (61pp)

L8 ANSWER 13 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-033946 [03] WPIDS
DNC C97-010497
TI- Poly-ribosyl ribitol phosphate vaccine against diphtheria, hepatitis B etc. - stabilised by presence of aluminium based adjuvant, has increased storage stability whilst maintaining same immune response.
DC B04 D16
IN ARMINJON, F; CARTIER, J R; MARCHALL, H L; CARTIER, J
PA (INMR) PASTEUR MERIEUX SERUMS & VACCINS; (INMR) PASTEUR MERIEUX SERUMS & VACCINS SA
CYC 71
PI WO 9637222 A1 961128 (9703)* FR 21 pp
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
FR 2734484 A1 961129 (9704) 10 pp
AU 9660086 A 961211 (9713)
NO 9705366 A 971121 (9809)
EP 828511 A1 980318 (9815) FR
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
SK 9701529 A3 980708 (9836)
ADT WO 9637222 A1 WO 96-FR791 960524; FR 2734484 A1 FR 95-6417 950524; AU 9660086 A AU 96-60086 960524; NO 9705366 A WO 96-FR791 960524, NO 97-5366 971121; EP 828511 A1 EP 96-917554 960524, WO 96-FR791 960524; SK 9701529 A3 WO 96-FR791 960524, SK 97-1529 960524
FDT AU 9660086 A Based on WO 9637222; EP 828511 A1 Based on WO 9637222
PRAI FR 95-6417 950524
AN 97-033946 [03] WPIDS
AB WO 9637222 A UPAB: 970129
New vaccine compsn. comprises:(a) 1 or more **antigens** which are **high** mol. **wt.** capsular polysaccharides of **Haemophilus influenzae** type b or poly-ribosyl-ribitol phosphate (PRP-T) coupled to the tetanus toxoid, and(b) an aluminium-based adjuvant which has a 0 point of charge of <7.2.

Also claimed is a method for the prodn. of the vaccine as above.

USE - The vaccine can be used against diphtheria, tetanus, whooping cough, hepatitis B, and poliomyelitis (claimed).

ADVANTAGE - The vaccine has better storage stability than when the aluminium adjuvant is aluminium hydroxide, whilst maintaining the same immune response.
Dwg.0/0

L8 ANSWER 14 OF 58 TOXLIT
AN 1997:30168 TOXLIT
DN CA-126-094782B
TI Vaccine composition containing polyribosylribitol phosphate and method for making same.
AU Arminjon F; Cartier J
SO (1996). PCT Int. Appl. PATENT NO. 96 37222 11/28/96 (Pasteur Merieux Serums Et Vaccins S.A.).
CY France
DT Patent
FS CA
LA French
OS CA 126:94782
EM 199703
AB A vaccine compn. contg. 1 or more **antigens** comprising the **high** mol. **wt.** capsular polysaccharide of the type b **Haemophilus influenza**, or polyribosylribitol phosphate, coupled to the tetanus toxoid and an aluminum-based adjuvant, wherein the aluminum-based adjuvant has, in its natural state, or following anion addn., a zero point of charge of <7.2. A method for making the vaccine compn. is also described. A vaccine compn. contained aluminum hydroxide 0.25 mg, PRP-T 10 mug, ADP and ATP 1 vaccinating dose each, phosphates 15 mumol, polio **antigen** type I, II, and III 40, 8, and 32 U resp., pertussis toxin 25 mug, buffer 0.125 mL, and water 0.5 mL.

DUPLICATE 8

L8 ANSWER 15 OF 58 MEDLINE
AN 97047678 MEDLINE
DN 97047678
TI Synthesis, characterization, and immunologic properties of detoxified lipooligosaccharide from nontypeable **Haemophilus influenzae** conjugated to proteins.
AU Gu X X; Tsai C M; Ueyama T; Barenkamp S J; Robbins J B; Lim D J
CS Vaccine Development Unit, Laboratory of Cellular Biology, National Institute of Deafness and Other Communication Disorders, NIH, Rockville, Maryland 20850, USA.. xgu@pop.nidcd.nih.gov
SO INFECTION AND IMMUNITY, (1996 Oct) 64 (10) 4047-53.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199701
EW 19970104

AB Nontypeable **Haemophilus influenzae** (**NTHi**
) is an important cause of **otitis media** in
children and of pneumonitis in adults with depressed resistance.
Lipooligosaccharide (LOS) is a major surface **antigen** of
NTHi and elicits bactericidal and opsonic antibodies. We
prepared detoxified LOS (dLOS) protein conjugates from **NTHi**
for use as experimental vaccines. LOS from **NTHi** 9274 was
treated with anhydrous hydrazine and had its toxicity reduced to
clinically acceptable levels. dLOS was bound to tetanus toxoid (TT)
or **high- molecular-weight** proteins (
HMPs) from **NTHi** through a linker of adipic acid
dihydrazide to form dLOS-TT or dLOS-**HMP**. The molar ratio
of the dLOS to protein carriers ranged from 26:1 to 50:1. The
antigenicity of the conjugates was similar to that of the LOS alone
as determined by double immunodiffusion. Subcutaneous or
intramuscular injection of the conjugates elicited a 28- to 486-fold
rise in the level of immunoglobulin G antibodies in mice to the
homologous LOS after two or three injections and a 169- to 243-fold
rise in the level of immunoglobulin G antibodies in rabbits after
two injections. The immunogenicity of the conjugates in mice and
rabbits was enhanced by formulation with monophosphoryl lipid A plus
trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies
induced complement-mediated bactericidal activity against the
homologous strain 9274 and prototype strain 3189. These results
indicate that a detoxified LOS-protein conjugate is a candidate
vaccine for **otitis media** and pneumonitis caused
by **NTHi**.

DUPLICATE 9

L8 ANSWER 16 OF 58 MEDLINE
AN 96333336 MEDLINE
DN 96333336
TI Identification of surface-exposed B-cell epitopes on **high**
molecular-weight adhesion proteins of nontypeable
Haemophilus influenzae.
AU Barenkam S J; St. Geme J W 3rd
CS Department of Pediatrics, St. Louis University School of Medicine,
Missouri, USA.
NC AI-21707 (NIAID)
DC-02873 (NIDCD)
SO INFECTION AND IMMUNITY, (1996 Aug) 64 (8) 3032-7.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199611
AB We previously reported that two surface-exposed **high-**
molecular-weight proteins, **HMW1** and
HMW2, expressed by a prototypic strain of nontypeable

Haemophilus influenzae (**NTHI**) mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to most nontypeable Haemophilus strains. We also reported that immunization with an **HMW1-HMW2** mixture modified the course of disease in an animal model of **otitis media**, suggesting the potential usefulness of these proteins as **NTHI** vaccine components. Identification of surface-accessible B-cell epitopes could be important to efforts to develop recombinant or synthetic peptide vaccines based upon these **high-molecular -weight** proteins. Thus, the purpose of the present study was to identify surface-accessible epitopes on the **HMW1** and **HMW2** proteins by using monoclonal antibodies (MAbs) and to determine the prevalence of these epitopes among the **high-molecular-weight** proteins expressed by heterologous nontypeable Haemophilus strains. MAbs were generated by immunizing mice with **high-molecular-weight** proteins purified from prototype strains and were screened by immunoelectron microscopy (IEM) for the ability to recognize surface epitopes. Two MAbs, designated AD6 and 10C5, that recognized surface epitopes by IEM were recovered. In order to map the epitopes recognized by these two MAbs, we constructed a set of **HMW1** and **HMW2** recombinant fusion proteins using the pGEMEX vectors and examined the reactivity of the MAbs with these fusion proteins. MAb AD6 recognized an epitope in both **HMW1** and **HMW2** which mapped to the last 75 amino acids at the carboxy termini of the two proteins. When examined for reactivity with heterologous strains, MAb AD6 recognized **high-molecular-weight** proteins in 75% of 125 unrelated nontypeable Haemophilus strains and, in addition, reacted with three of three such strains when examined by IEM. MAb 10C5 recognized an epitope that mapped to a 155-amino-acid segment near the carboxy terminus of **HMW1**. This epitope was adjacent to but distinct from the AD6 epitope and was absent from **HMW2**. The 10C5 epitope was expressed by 40% of the AD6 reactive strains. Identification of shared surface-exposed epitopes on the **high-molecular-weight** adhesion proteins suggests the possibility of developing recombinant or synthetic peptide-based vaccines protective against disease caused by the majority of **NTHI** strains.

L8 ANSWER 17 OF 58 MEDLINE
AN 96238995 MEDLINE
DN 96238995
TI Evaluation of purified UspA from Moraxella catarrhalis as a vaccine in a murine model after active immunization.
AU Chen D; McMichael J C; VanDerMeid K R; Hahn D; Mininni T; Cowell J; Eldridge J
CS Lederle-Praxis Biologicals, West Henrietta, New York 14586-9728,

USA.
SO INFECTION AND IMMUNITY, (1996 Jun) 64 (6) 1900-5.
Journal code: G07. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199610
AB Moraxella catarrhalis causes **otitis media**, laryngitis, and respiratory infections in humans. A **high** -molecular-**weight** outer membrane protein from this bacterium named ubiquitous surface protein A (UspA) is present on all isolates. A monoclonal antibody (MAb) to UspA that recognizes a conserved epitope of this protein has been shown to promote pulmonary clearance of bacteria in passively immunized mice. In the present study, M. catarrhalis heterologous isolates were screened by dot blot with a panel of four additional MAbs specific for surface-exposed epitopes of UspA from M. catarrhalis isolate 035E. Three of the MAbs were specific for 035E, and the fourth reacted with 17 (74%) of the 23 isolates tested. Thus, UspA contains highly conserved, semiconserved, and variable surface-exposed epitopes. The UspA was purified from the 035E isolate by ion-exchange and size-exclusion chromatography, formulated with the adjuvant QS-21, and used to immunize BALB/c mice. Upon pulmonary challenge with either 035E or the heterologous isolate TTA24, significantly fewer bacteria were recovered from the lungs of immunized mice 6 h postchallenge than from control mice. The immune sera from mice or guinea pigs contained high titers of antibodies to the homologous isolate and heterologous isolates in a whole-bacterial-cell enzyme-linked immunosorbent assay. Sera against UspA, whether prepared in mice or guinea pigs, had complement-dependent bactericidal activity toward homologous and 11 heterologous M. catarrhalis isolates. These results indicate that the conserved epitopes of the UspA are highly immunogenic and elicit broadly reactive and biologically functional antibodies. UspA may offer protection against M. catarrhalis infections and is being further evaluated as a vaccine candidate.

DUPLICATE 10

L8 ANSWER 18 OF 58 MEDLINE
AN 96178615 MEDLINE
DN 96178615
TI Immunization with **high**-molecular-**weight** adhesion proteins of nontypeable **Haemophilus influenzae** modifies experimental **otitis media** in chinchillas.
AU Barenkamp S J
CS Department of Pediatrics, St. Louis University School of Medicine, Missouri, USA.
NC AI-21707 (NIAID)

SO INFECTION AND IMMUNITY, (1996 Apr) 64 (4) 1246-51.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199607

AB Prevention of nontypeable **Haemophilus influenzae** **otitis media** by vaccination is an important health care goal. Proteins important in bacterial adherence deserve consideration as potential vaccine candidates. Two colleagues and I previously identified a family of immunogenic **high-molecular-weight** proteins important in adherence of nontypeable **H. influenzae** to human epithelial cells (J.W. St. Geme III, S. Falkow, and S.J. Barenkamp, Proc. Natl. Acad. Sci. USA, 90:2875-2879, 1993). In the work described here, I determined whether immunization with two such adherence proteins, **HMW1** and **HMW2**, purified from prototype nontypeable Haemophilus strain 12, would modify the course of experimental **otitis media** caused by the homologous strain. Chinchillas received three monthly subcutaneous injections with 40 microgram of an **HMW1/HMW2** protein mixture in Freud's adjuvant. One month after the last injection, animals were challenged by intrabullar inoculation with 300 CFU of nontypeable **H. influenzae** 12. Infection developed in five of five control animals versus 5 of 10 immunized animals (P = 0.08, Fisher exact, one-tailed). Among infected animals, bacterial counts in middle ear fluid specimens 7 days postchallenge were significantly greater in control animals than in immunized animals (P = 0.014, Mann-Whitney U test). Serum antibody titers following immunization were comparable in uninfected and infected animals. However, infection in immunized animals was uniformly associated with the appearance of bacteria downregulated in expression of the **high-molecular-weight** proteins, suggesting bacterial selection in response to immunologic pressure. Although protection following immunization was incomplete, these data suggest that the **high-molecular-weight** adhesion proteins are potentially important protective **antigens** which might represent one component of a multicomponent nontypeable Haemophilus vaccine.

DUPLICATE 11

L8 ANSWER 19 OF 58 MEDLINE
AN 96332658 MEDLINE
DN 96332658
TI Identification of a second family of **high**-molecular-**weight** adhesion proteins expressed by non-typable **Haemophilus influenzae.**
AU Barenkamp S J; St. Geme J W 3rd
CS Department of Pediatrics, St. Louis University School of Medicine,

Cardinal Glennon Children's Hospital, Missouri 63104, USA..
barenksj@sluvca.slu.edu
NC AI-21707 (NIAID)
SO MOLECULAR MICROBIOLOGY, (1996 Mar) 19 (6) 1215-23.
Journal code: MOM. ISSN: 0950-382X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U38617
EM 199611
AB We previously reported that two surface-exposed **high-molecular-weight** proteins, **HMW1** and **HMW2**, expressed by a prototypic strain of non-typable **Haemophilus influenzae** (**NTHI**), mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to 70-75% of **NTHI** strains. **NTHI** strains that lack **HMW1/HMW2**-like proteins remain capable of efficient attachment to cultured human epithelial cells, suggesting the existence of additional adhesion **molecules**. We reasoned that characterization of **high-molecular-weight** immunogenic proteins from an **HMW1/HMW2**-deficient strain might identify additional adhesion proteins. A genomic library was prepared in lambda EMBL3 with chromosomal DNA from non-typable Haemophilus strain 11, a strain that lacks **HMW1/HMW2**-like proteins. The library was screened immunologically with convalescent serum from a child naturally infected with strain 11, and phage clones expressing **high-molecular-weight** recombinant proteins were identified by Western blot analysis. One clone was identified that expressed a protein with an apparent **molecular** mass greater than 200 kDa. Transformation of non-adherent Escherichia coli strain DH5 alpha with plasmids containing the genetic locus encoding this protein gave rise to E. coli transformants that adhered avidly to Chang conjunctival cells. Subcloning and mutagenesis studies localized the DNA conferring the adherence phenotype to a 4.8 kbp fragment, and nucleotide sequence analysis further localized the gene encoding the adhesion protein to a 3.3 kbp open reading frame predicted to encode a protein of 114 kDa. The gene was designated hia for **Haemophilus influenzae adhesin**. Southern analysis revealed an hia homologue in 13 of 15 **HMW1/HMW2**-deficient non-typable **H. influenzae** strains. In contrast, the hia gene was not present in any of 23 non-typable **H. influenzae** strains which expressed **HMW1/HMW2**-like proteins. Identification of this second family of **high-molecular-weight** adhesion proteins suggests the possibility of developing vaccines based upon a

combination of **HMW1/HMW2**-like proteins and Hia-like proteins which would be protective against disease caused by most or all non-typable **H. influenzae**.

L8 ANSWER 20 OF 58 LIFESCI COPYRIGHT 1999 CSA
AN 97:95398 LIFESCI
TI **High** molecular **weight** surface proteins of non-typeable Haemophilus
CS ST. LOUIS UNIVERSITY
SO (1996) . US Patent 5549897; US Cl. 424/256.1 435/851 530/350.
DT Patent
FS A
LA English
AB **High molecular weight** surface proteins of non-typeable **Haemophilus influenzae** which exhibit immunogenic properties and genes encoding the same are described. Specifically, genes coding for two immunodominant **high molecular weight** proteins, **HMW1** and **HMW2**, have been cloned, expressed and sequenced, while genes coding for high **molecular** proteins **HMW3** and **HMW4** have been cloned, expressed and partially sequenced.

L8 ANSWER 21 OF 58 PROMT COPYRIGHT 1999 IAC

AN 96:595094 PROMT
TI **Haemophilus influenzae**: "Synthesis, Characterization, and Immunologic Properties of Detoxified Lipooligosaccharide from Nontypeable **Haemophilus influenzae** Conjugated to Proteins."
SO Vaccine Weekly, (11 Nov 1996) pp. N/A.
ISSN: 1074-2921.
LA English
WC 317
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB Gu, X.X.; Tsai, C.M.; Ueyama, T.; Barenkamp, S.J.; Robbins, J.B.; Lim, D.J. Infection and Immunity, October 1996;64(10):4047-4053. According to the authors' abstract of an article published in Infection and Immunity, "Nontypeable **Haemophilus influenzae** (**NTHi**) is an important cause of **otitis media** in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a major surface **antigen** of **NTHi** and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from **NTHi** for use as experimental vaccines. LOS from **NTHi** 9274 was treated with anhydrous hydrazine and had its toxicity reduced to clinically acceptable levels, dLOS was bound to tetanus toxoid (TT) or **high-molecular-weight** proteins (

HMPs) from **NTHi** through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-**HMP**. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion. Subcutaneous or intramuscular injection of the conjugates elicited a 28- to 486-fold rise in the level of immunoglobulin G antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of immunoglobulin G antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for **otitis media** and pneumonitis caused by **NTHi**." The corresponding author for this study is: XX Gu, Nidocd, NIH, Vaccine Dev Unit, Lab Cellular Biol, 5 Res CT, RM 2A31, Rockville, MD 20850 USA. For subscription information for this journal contact the publisher: Amer Soc Microbiology, 1325 Massachusetts Avenue, NW, Washington, DC 20005-4171.

L8 ANSWER 22 OF 58 PROMT COPYRIGHT 1999 IAC

AN 96:590170 PROMT

TI **Haemophilus influenzae** "Synthesis, Characterization, and Immunologic Properties of Detoxified Lipooligosaccharide from Nontypeable **Haemophilus influenzae** Conjugated to Proteins."

SO Disease Weekly Plus, (11 Nov 1996) pp. N/A.

LA English

WC 317

FULL TEXT IS AVAILABLE IN THE ALL FORMAT

AB Gu, X.X.; Tsai, C.M.; Ueyama, T.; Barenkamp, S.J.; Robbins, J.B.; Lim, D.J.
Infection and Immunity, October 1996;64(10):4047-4053.
According to the authors' abstract of an article published in Infection and Immunity, "Nontypeable **Haemophilus influenzae** (**NTHi**) is an important cause of **otitis media** in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a major surface **antigen** of **NTHi** and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from **NTHi** for use as experimental vaccines. LOS from **NTHi** 9274 was treated with anhydrous hydrazine and had its toxicity reduced to clinically acceptable levels, dLOS was bound to tetanus toxoid (TT) or **high-molecular-weight** proteins (

HMPs) from **NTHi** through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-**HMP**. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion. Subcutaneous or intramuscular injection of the conjugates elicited a 28- to 486-fold rise in the level of immunoglobulin G antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of immunoglobulin G antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for **otitis media** and pneumonitis caused by **NTHi**." The corresponding author for this study is: XX Gu, Nidocd, NIH, Vaccine Dev Unit, Lab Cellular Biol, 5 Res CT, RM 2A31, Rockville, MD 20850 USA. For subscription information for this journal contact the publisher: Amer Soc Microbiology, 1325 Massachusetts Avenue, NW, Washington, DC 20005-4171.

DUPLICATE 12

L8 ANSWER 23 OF 58 MEDLINE
AN 95310001 MEDLINE
DN 95310001
TI Binding of **Haemophilus influenzae** to purified mucins from the human respiratory tract.
AU Davies J; Carlstedt I; Nilsson A K; Hakansson A; Sabharwal H; van Alphen L; van Ham M; Svanborg C
CS Department of Medical and Physiological Chemistry, Lund University, Sweden..
SO INFECTION AND IMMUNITY, (1995 Jul) 63 (7) 2485-92.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199509
AB Mucins are **high**-molecular-**weight** glycoproteins and major constituents of the mucus layer which covers the airway surface. We have studied the interactions between bacteria, mucins, and epithelial cells from the human respiratory tract. Nontypeable strains of **Haemophilus influenzae** were found to bind to purified airway mucins in suspension and on solid phase. Mucins in suspension inhibited the attachment of these strains to nasopharyngeal epithelial cells, while mucin coating of the cells enhanced their binding. In contrast, strains of Streptococcus pneumoniae and encapsulated and other nontypeable **H.**

Searcher : Shears 308-4994

influenzae strains failed to interact with mucins. These **H. influenzae** strains used other strategies for adherence to epithelial cells. The type b strain 770235 attached via fimbriae but also expressed a subcapsular **adhesin** that was detected in a capsule- and fimbria-defective mutant. Mucin pretreatment of these bacteria did not inhibit adherence, but mucin pretreatment of epithelial cells inhibited adherence, probably by shielding of the receptors for these **adhesins**. Non-mucin-binding nontypeable and encapsulated **H. influenzae** strains would, therefore, adhere only after disruption of the mucus layer and exposure of cellular receptors. Differences in tissue toxicity and invasiveness among **H. influenzae** strains may also be influenced by the mucin interactions of the strains.

L8 ANSWER 24 OF 58 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 95:60968 SCISEARCH
GA The Genuine Article (R) Number: QA649
TI HUMAN IMMUNE-RESPONSE AGAINST OUTER-MEMBRANE PROTEINS OF MORAXELLA (BRANHAMELLA) CATARRHALIS DETERMINED BY IMMUNOBLOTTING AND ENZYME-IMMUNOASSAY
AU HELMINEN M E; BEACH R; MACIVER I; JAROSIK G; HANSEN E J; LEINONEN M (Reprint)
CS NATL PUBL HLTH INST, DEPT OULU, POB 310, SF-90101 OULU, FINLAND (Reprint); NATL PUBL HLTH INST, DEPT OULU, SF-90101 OULU, FINLAND; NATL PUBL HLTH INST, SF-00300 HELSINKI, FINLAND; UNIV TEXAS, SW MED CTR, DEPT MICROBIOL, DALLAS, TX, 75235
CYA FINLAND; USA
SO CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, (JAN 1995) Vol. 2, No. 1, pp. 35-39.
ISSN: 1071-412X.
DT Article; Journal
FS CLIN
LA ENGLISH
REC Reference Count: 42
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The role of Moraxella (Branhamella) catarrhalis as a respiratory tract pathogen is increasingly recognized. We looked at the human immune response against individual outer membrane proteins of M. catarrhalis and against the 81-kDa CopB protein, which has previously been shown to be a target far protective antibodies. Paired serum samples from six elderly patients with pneumonia were tested by Western blot (immunoblot) analysis by using outer membrane vesicles of M. catarrhalis 035E as **antigen**. All of the six convalescent-phase serum samples reacted with a protein which migrated at the position of the CopB protein and with a **high** -molecular-**weight** protein of M. catarrhalis; three serum samples also reacted with a 34-kDa outer membrane protein. Paired serum samples from 18 patients, 10 of which had M. catarrhalis

infection on the basis of previous serology results, were tested by enzyme immunoassay (EIA) with the CopB protein and whole cells of M. catarrhalis 035E as **antigens**. Nine patients showed a significant rise in EIA titer between acute- and convalescent-phase sera when whole bacterial cells were used as **antigens**. Six (67%) patient samples that were positive by the EIA with the whole-cell **antigen** were also positive by the EIA with the CopB **antigen**, and six of nine patient samples negative by the EIA with the whole-cell **antigen** were also negative by the EIA with the CopB **antigen**. These results suggest that both the CopB and a **high**-molecular-**weight** protein are major targets of the immune response against M. catarrhalis, and further studies with greater amounts of patient materials are needed to elucidate the usefulness of CopB as an **antigen** in etiologic studies.

L8 ANSWER 25 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-15222 BIOTECHDS
TI New immunogenic **high** molecular **weight** proteins of non-typeable Haemophilus; **Haemophilus influenza** recombinant protein HMW1, HMW2, HMW3 and HMW4 production for use as a native or recombinant vaccine against sinusitis, bronchitis, **otitis media**, etc.
PA Barenkamp S J
PI WO 9421290 29 Sep 1994
AI WO 94-US2550 15 Mar 1994
PRAI US 93-38682 16 Mar 1993
DT Patent
LA English
OS WPI: 94-316665 [39]
AN 94-15222 BIOTECHDS
AB A vaccine against disease caused by non-typeable (nt) **Haemophilus influenzae**, including **otitis media**, sinusitis and bronchitis, comprises an effective amount of a **high** mol.**wt**. protein (I) of nt **H. influenzae**, especially HMW1, HMW2, HMW3 or HMW4, or their immunologically active variants or fragments or synthetic peptides, and a physiological adjuvant. The DNA sequences of the gene encoding the **H. influenza** HMW1 and HM2 and the partial sequences of HMW3 and HMW4 proteins are disclosed (4,116, 4,937, 4,287 and 4,702 bp, respectively) together with derived protein sequences. (I) are useful in vaccines against diseases not controlled by **H. influenza** type b vaccines. (I) are present on most nt Haemophilus spp. so should be useful in a universal Haemophilus vaccine. Apart from use as vaccine **antigens**, (I) can be used in conjugate vaccines with protective **H. influenza** type b polysaccharides against meningitis. Nt

Haemophilus strain 12 was digested with SauIIIA and ligated into phage lambda. Phage lambda was grown in Escherichia coli LE392 and clones recognized by serum containing a high antibody titer against (I) were isolated. (127pp)

L8 ANSWER 26 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1995:790 BIOSIS
DN PREV199598015090
TI Early events in the pathogenesis of **Haemophilus influenzae** disease.
AU St Geme, Joseph W. Iii
CS Dep. Mol. Microbiol., Washington Univ. Sch. Med., 660 S. Euclid Ave., Box 8230, St. Louis, MO 63110 USA
SO Miller, V. L. [Editor]; Kaper, J. B. [Editor]; Portnoy, D. A. [Editor]; Isberg, R. R. [Editor]. (1994) pp. 157-172. Molecular genetics of bacterial pathogenesis: A tribute to Stanley Falkow. Publisher: American Society for Microbiology (ASM) Books Division, 1325 Massachusetts Ave. NW, Washington, DC 20005-4171, USA. ISBN: 1-55581-082-9.
DT Book; General Review
LA English

DUPLICATE 14

L8 ANSWER 27 OF 58 MEDLINE
AN 95012637 MEDLINE
DN 95012637
TI Localization of **high**-molecular-**weight** adhesion proteins of nontypeable **Haemophilus influenzae** by immunoelectron microscopy.
AU Bakaletz L O; Barenkamp S J
CS Department of Otolaryngology, Ohio State University College of Medicine, Columbus..
NC AI 21707 (NIAID)
SO INFECTION AND IMMUNITY, (1994 Oct) 62 (10) 4460-8.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199501
AB A family of **high-molecular-weight** (**HMW**) surface-exposed proteins important in the attachment of nontypeable **Haemophilus influenzae** (**NTHi**) to human epithelial cells was previously identified (J. W. St. Geme III, S. Falkow, and S. J. Barenkamp, Proc. Natl. Acad. Sci. USA 90:2875-2879, 1993). In the present investigation, indirect immunogold labeling and electron microscopy were used to localize these proteins on three clinical isolates of **NTHi**, mutants deficient in expression of one or both **HMW** proteins, and embedded sections of human oropharyngeal cells after incubation with

NTHi strain 12. The filamentous material comprising the proteins was labeled with monoclonal antibodies directed against two prototype **HMW** proteins (**HMW1** and **HMW2**) of prototype **NTHi** strain 12. Gold labeling was observed as a cap or discrete aggregate off one pole or centrally along one long axis of the bacterial cell. Heavily labeled, non-bacterial-cell-associated, disk-like aggregates of the **HMW** proteins were frequently noted in both bacterial preparations as well as in association with the oropharyngeal cell surface and intracellularly. Mutants demonstrated diminished labeling or an absence thereof, respectively, which correlated well with their previously demonstrated reduced ability or inability to adhere to Chang conjunctival epithelial cells in vitro. The Haemophilus **HMW** proteins share antigenic determinants with and demonstrate amino acid sequence similarity to the filamentous hemagglutinin protein of Bordetella pertussis, a critical **adhesin** of that organism. The studies presented here demonstrate that the Haemophilus proteins and B. pertussis filamentous hemagglutinin show impressive morphologic and perhaps additional functional similarity.

L8 ANSWER 28 OF 58 LIFESCI COPYRIGHT 1999 CSA
AN 95:7493 LIFESCI
TI **High**-molecular-**weight** proteins of nontypeable **Haemophilus influenzae** mediate bacterial adhesion to cellular proteoglycans
AU Noel, G.J.; Love, D.C.; Mosser, D.M.
CS Dep. Pediatr., Div. Pediatr. Infect. Dis. and Immunol., Cornell Univ. Med. Coll., New York, NY 10021, USA
SO INFECT. IMMUN., (1994) vol. 62, no. 9, pp. 4028-4033. ISSN: 0019-9567.
DT Journal
FS J
LA English
SL English
AB A family of **high-molecular-weight** (**HMW**) surface-exposed proteins of nontypeable **Haemophilus influenzae** (NT H. **influenzae**) mediated adherence of these organisms to human epithelium. To better understand the **molecular** basis for this adherence, the role of glycosaminoglycans (GAGs), substances commonly expressed on cell surfaces, was examined. Bacterial adherence to cells with specific deficiencies in GAG biosynthesis was measured. **HMW** protein-dependent bacterial adherence to normal cells was significantly greater than adherence to cells deficient in sulfated GAGs or to cells deficient in heparan sulfate but overexpressing chondroitin sulfate. Cells expressing undersulfated heparan sulfate exhibited intermediate levels of bacterial adherence. The addition of exogenous dextran sulfate or heparin inhibited over 70% of the adherence of NT H.

influenzae to normal cells, whereas hyaluronic acid and chondroitin sulfate tested at the same concentration (100 mu g/ml) inhibited bacterial adherence by less than 11%. Treatment of cells with heparinase significantly reduced bacterial adherence. Following electrophoretic separation, **HMW** proteins were shown to bind directly to radiolabeled heparin. These results indicate that **HMW** protein-dependent adherence of NT **H. influenzae** is mediated by cellular sulfated GAGs and that heparan sulfate may be the predominant GAG involved in this process. However, the decreased adherence of bacteria to cells expressing undersulfated heparan sulfate and the inhibition of bacterial adherence by the addition of exogenous dextran sulfate suggest that bacterial adhesion to mammalian cells is likely to be influenced by a variety of factors, including the degree of sulfation and the specificity of the carbohydrate moieties contained in the cellular proteoglycans.

DUPLICATE 15

L8 ANSWER 29 OF 58 MEDLINE
AN 94341895 MEDLINE
DN 94341895
TI The HMW1 **adhesin** of nontypeable **Haemophilus influenzae** recognizes sialylated glycoprotein receptors on cultured human epithelial cells.
AU St. Geme J W 3rd
CS Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri 63110.
NC HD-29678 (NICHD)
SO INFECTION AND IMMUNITY, (1994 Sep) 62 (9) 3881-9.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199411
AB Disease due to nontypeable **Haemophilus influenzae** begins with colonization of the upper respiratory tract mucosa. We recently reported that two surface-exposed **high-molecular-weight** proteins (**HMW1** and **HMW2**) expressed by a prototypic strain of nontypeable **H. influenzae** mediate attachment to cultured epithelial cells. In the present study, we examined the nature of the epithelial cell receptor with which **HMW1** interacts. Both proteinase K pretreatment and periodate oxidation of epithelial monolayers resulted in a marked decrease in **HMW1**-mediated binding, suggesting interaction with a glycoprotein structure. Treatment with peptide-N-glycosidase F produced a similar decrease in attachment and thereby provided further evidence for this conclusion. Desialylation of the epithelial cell surface also reduced binding, implying the presence of sialic acid in the

receptor structure. Furthermore, lectins specific for terminal alpha 2-3-linked sialic acid were capable of inhibiting **HMW1** -mediated attachment. In summary, our results indicate that the **HMW1 adhesin** interacts with a glycoprotein receptor containing N-linked oligosaccharide chains with sialic acid in an alpha 2-3 configuration.

DUPLICATE 16

L8 ANSWER 30 OF 58 MEDLINE
AN 94149333 MEDLINE
DN 94149333
TI **High**-molecular-**weight** surface-exposed proteins of **Haemophilus influenzae** mediate binding to macrophages.
AU Noel G J; Barenkamp S J; St Geme J W 3rd; Haining W N; Mosser D M
CS Division of Pediatric Infectious Diseases and Immunology, Cornell University Medical College, New York, New York..
NC AI-30063 (NIAID)
SO JOURNAL OF INFECTIOUS DISEASES, (1994 Feb) 169 (2) 425-9. Journal code: IH3. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199405
AB The **molecular** basis for direct bacteria-macrophage interactions that distinguishes nontypeable (NT) **Haemophilus influenzae** from type b organisms is not known. Because of similarities between filamentous hemagglutinin (FHA) **adhesin** of Bordetella pertussis and **high-molecular-weight** (**HMW**) proteins commonly expressed by NT **H. influenzae**, the role that **HMW** proteins play in determining NT **H. influenzae** -macrophage interactions was assessed. In tests with genetically engineered organisms, **HMW** protein-expressing bacteria bound significantly better than isogenic **HMW** protein-deficient bacteria to macrophages. **HMW** protein-dependent binding to macrophages is trypsin-sensitive, is independent of divalent cations, does not occur via the leukocyte integrin CD11b/CD18, and is not affected by galactose-containing carbohydrates. Organisms bound via **HMW** proteins remain largely extracellular and viable. Like FHA of Bordetella organisms, **HMW** proteins mediate binding of NT **H. influenzae** to macrophages. However, unlike the interaction determined by FHA, this interaction is characteristically one of adhesion and requires additional serum opsonization for efficient killing of bacteria by macrophages.

L8 ANSWER 31 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 17

AN 94375620 EMBASE
DN 1994375620
TI Adherence and invasion of **Haemophilus influenzae**

AU van Alphen L.; van Ham S.M.
CS Department of Medical Microbiology, University of Amsterdam, Academic Medical Centre, Meibergdreef 15,NL-1105 AZ Amsterdam, Netherlands

SO Reviews in Medical Microbiology, (1994) 5/4 (245-255).
ISSN: 0954-139X CODEN: RMEMER
CY United Kingdom
DT Journal; General Review
FS 004 Microbiology
LA English
SL English

AB Adherence of **Haemophilus influenzae** to epithelial cells plays a central role in colonization and is the first step in infection. It allows **H. influenzae** to establish itself, adapt to local conditions required for localized growth of the bacteria, and resist mechanical clearance mechanisms of the host. Bound to the cells the organism can evoke localized effects on the tissue which may lead to an inflammatory reaction, or the penetration of the bacteria between the cells into the tissues underlying the epithelium. Various **adhesins**, including fimbriae and **high**-molecular-**weight** outer membrane proteins, promote binding to different receptors, resulting in tissue tropism. A variety of other bacterial determinants, including the capsule and LPS, also contribute to the establishment and course of the infection. The occurrence of random and reversible fimbrial phase variation ensures the generation of a genetically and phenotypically diverse bacterial population. The diversity allows properly equipped **H. influenzae** cells (fimbriated on epithelia and non-fimbriated in the blood) to be present at random in the bacterial population, not selected for a particular fimbrial phenotype. Subsequently, natural conditions will drive selection of a particular phenotype required for survival in a specific host tissue site (mucosa, blood, etc).

L8 ANSWER 32 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1994:248909 BIOSIS
DN PREV199497261909
TI **Molecular** characterization of nontypable **Haemophilus influenzae** (**NTHI**) variant strains down-regulated in expression of **high molecular weight** (**HMW**) adhesion proteins.

AU Barenkamp, Stephen J.
CS St. Louis Univ. Sch. Med., Pediatric Res. Inst., St. Louis, MO USA

SO Pediatric Research, (1994) Vol. 35, No. 4 PART 2, pp. 173A.

Meeting Info.: 104th Annual Meeting of the American Pediatric Society and the 63rd Annual Meeting of the Society for Pediatric Research Seattle, Washington, USA May 2-5, 1994
ISSN: 0031-3998.
DT Conference
LA English

L8 ANSWER 33 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 93-14467 BIOTECHDS
TI **High** molecular **weight** protein of non-typeable Haemophilus;
recombinant HMW1, HMW2, HMW3 and HMW4 protein immunogen production by vector expression for use in recombinant vaccine
PA Barenkamp S J
PI WO 9319090 30 Sep 1993
AI WO 93-US2166 16 Mar 1993
PRAI GB 92-5704 16 Mar 1992
DT Patent
LA English
OS WPI: 93-320683 [40]
AN 93-14467 BIOTECHDS
AB An isolated and purified gene (I) encoding a **high** mol. **wt.** protein (II) (preferably HMW1, HMW2, HMW3 or HMW4 or their variants or fragments) of a non-typeable Haemophilus strain (NTHS) is claimed. (II) is useful as an immunogen in native or recombinant vaccines against NTHS diseases. The DNA sequence of (I) and the protein sequences of (II) are disclosed. The following are also claimed: (1) a purified and isolated gene cluster comprising (I) encoding (II) and at least 1 downstream expression control sequence, especially (I) encoding HMW1 and HMW2 and 2 downstream control sequences; (2) HMW1 and HMW2 of mol.wt. 125,000 and 120,000, respectively, useful for NTHS disease prevention; (3) HMW1, HMW2, HMW3 or HMW4 which is antigenically related to the filamentous hemagglutinin surface protein of Bordetella pertussis; (4) a conjugate of (I) linked to a hapten, **antigen** or polysaccharide (protective against **Haemophilus influenzae** type b) for eliciting an immune response to the hapten, **antigen** or polysaccharide; and (5) a synthetic peptide of protein sequence (HMW1, HMW2, HMW3 or HMW4) corresponding to at least 1 protective epitope of (II) of **H. influenzae.** (96pp)

L8 ANSWER 34 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 93-320683 [40] WPIDS
CR 94-316665 [39]
DNC C93-142729
TI **High** molecular **weight** surface proteins - of non-typeable haemophilus which exhibit immunogenic properties.
DC B04 D16

IN BARENKAMP, S J; ST, GEME J W
PA (UYSL-N) UNIV ST LOUIS; (UNIW) UNIV WASHINGTON; (BARE-I) BARENKAMP S J; (INRM) INSERM INST NAT SANTE & RECH MEDICALE
CYC 27
PI WO 9319090 A1 930930 (9340)* EN 96 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU BR CA FI JP KR NO RU UA US
AU 9339168 A 931021 (9407)
NO 9403431 A 941110 (9505)
EP 632814 A1 950111 (9506) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
FI 9404273 A 941115 (9506)
JP 07506248 W 950713 (9536) 29 pp
AU 669360 B 960606 (9630)
US 5549897 A 960827 (9640) 100 pp
EP 632814 A4 960313 (9642)
US 5603938 A 970218 (9713) 100 pp
BR 9306109 A 971118 (9802)
JP 2810235 B2 981015 (9846) 115 pp
ADT WO 9319090 A1 WO 93-US2166 930316; AU 9339168 A AU 93-39168 930316; NO 9403431 A WO 93-US2166 930316, NO 94-3431 940915; EP 632814 A1 EP 93-908295 930316, WO 93-US2166 930316; FI 9404273 A WO 93-US2166 930316, FI 94-4273 940915; JP 07506248 W JP 93-516604 930316, WO 93-US2166 930316; AU 669360 B AU 93-39168 930316; US 5549897 A US 93-38682 930316; EP 632814 A4 EP 93-908295 ; US 5603938 A WO 93-US2166 930316, US 94-302832 941005; BR 9306109 A BR 93-6109 930316, WO 93-US2166 930316; JP 2810235 B2 JP 93-516604 930316, WO 93-US2166 930316
FDT AU 9339168 A Based on WO 9319090; EP 632814 A1 Based on WO 9319090; JP 07506248 W Based on WO 9319090; AU 669360 B Previous Publ. AU 9339168, Based on WO 9319090; US 5603938 A Based on WO 9319090; BR 9306109 A Based on WO 9319090; JP 2810235 B2 Previous Publ. JP 07506248, Based on WO 9319090
PRAI GB 92-5704 920316
AN 93-320683 [40] WPIDS
CR 94-316665 [39]
AB WO 9319090 A UPAB: 961025
An isolated and purified gene exceeding a **high** mol. **wt.** (HMV) protein (I) of a non-tyeable Haemophilis strain (HP).

Also claimed are: (A) a purified and isolated gene cluster comprising a nucleotide sequence (NS) for a structural gene encoding (I) of a non-typeable HP; and more than 1 downstream NS for on accessory gene for affecting expression of a gene product fully enclosed by the structural gene. (B) (I) of non-typeable HP encoded by a gene as above, or its variant or fragment retaining the immunological ability to protect against disease caused by a non-typeable HP; (C) on isolated and purified (I) of non-typeable HV filaments haemoglutinin surface protein of Bordetella pertussis, (D)

a conjugate comprising (I) linked to anantigen, hapten or polysaccharide for elicting on immune response to the **antigen**, hapten or polysaccharide; and (E) a synthetic peptide having on aminoacid sequence corresponding to more than 1 protective epitope of a HMW protein of non-typeable **H. influenzae**.

ADVANTAGE - With the isolation of and purification of (I), it is possible to determine the major protective epitopes by conventional epitope mapping and synthesise peptide corresponding to these determinants to be incorporated in fully synthetic or recombinant vaccines

Dwg.0/10

Dwg.0/10

ABEQ US 5549897 A UPAB: 961007

A vaccine against disease caused by non-typeable **Haemophilus influenzae**, including **otitis media**, sinusitis and bronchitis, comprising an effective amount of a **high molecular weight** protein of non-typeable **Haemophilus influenzae** which is protein **HMW1** and/or **HMW2** and a physiological carrier therefor.

Dwg.0/10

ABEQ US 5603938 A UPAB: 970326

A 1536 amino acid (sequence given in the specification) **high** molecular **weight** non-typeable **Haemophilus influenzae** surface protein and a 5116 base pair DNA sequence (also given in the specification) are new.

Dwg.0/10

L8 ANSWER 35 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD

AN 93-093726 [11] WPIDS

DNN N93-071760 DNC C93-041417

TI Antigenic proteins derived form Moraxella catarrhalis outer membranes - useful for diagnosing and treating M. catarrhalis infections.

DC B04 D16 S03

IN HANSEN, E J; HELMINEN, M; MACIVER, I

PA (TEXA) UNIV TEXAS SYSTEM; (TEXA) UNIV TEXAS; (AMCY) AMERICAN CYANAMID CO

CYC 38

PI WO 9303761 A1 930304 (9311)* EN 73 pp

RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA SE

W: AT AU BB BG BR CA CH CS DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO PL RO RU SD SE US

AU 9224878 A 930316 (9328)

NO 9400502 A 940328 (9422)

FI 9400681 A 940407 (9424)

EP 612250 A1 940831 (9433) EN

R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL SE

JP 07501210 W 950209 (9515)
AU 666329 B 960208 (9613)
EP 612250 B1 960724 (9634) EN 29 pp
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL SE
DE 69212495 E 960829 (9640)
US 5552146 A 960903 (9641) 15 pp
ES 2092696 T3 961201 (9704)
US 5599693 A 970204 (9711) 17 pp
US 5759813 A 980602 (9829)

ADT WO 9303761 A1 WO 92-US6869 920814; AU 9224878 A AU 92-24878 920814; NO 9400502 A WO 92-US6869 920814, NO 94-502 940214; FI 9400681 A WO 92-US6869 920814, FI 94-681 940214; EP 612250 A1 EP 92-918273 920814, WO 92-US6869 920814; JP 07501210 W WO 92-US6869 920814, JP 93-504481 920814; AU 666329 B AU 92-24878 920814; EP 612250 B1 EP 92-918273 920814, WO 92-US6869 920814; DE 69212495 E DE 92-612495 920814, EP 92-918273 920814, WO 92-US6869 920814; US 5552146 A US 91-745591 910815; ES 2092696 T3 EP 92-918273 920814; US 5599693 A Div ex US 91-745591 910815, US 95-450002 950525; US 5759813 A Cont of US 91-745591 910815, Cont of WO 92-US6869 920814, US 94-193150 940919

FDT AU 9224878 A Based on WO 9303761; EP 612250 A1 Based on WO 9303761; JP 07501210 W Based on WO 9303761; AU 666329 B Previous Publ. AU 9224878, Based on WO 9303761; EP 612250 B1 Based on WO 9303761; DE 69212495 E Based on EP 612250, Based on WO 9303761; ES 2092696 T3 Based on EP 612250; US 5759813 A Cont of US 5552146

PRAI US 91-745591 910815; US 95-450002 950525; US 94-193150 940919

AN 93-093726 [11] WPIDS

AB WO 9303761 A UPAB: 970612

Compsn. contains a purified protein or peptide **antigen** (Ag) that includes an epitope immunologically cross-reactive with the 30 kD, 80 kD or **high mol. wt.** (**HMW**) outer-membrane proteins (OMP) of Moraxella catarrhalis.

Also new are (1) DNA segments (I) encoding Ag; (2) recombinant vectors and host cells contg. (I); (3) antibodies (Ab) against Ag and (4) kits for detecting Ag or Ab.

Ag is pref. one of the specified OMP, or a peptide (of 10-50 amino acids) contg. an appropriate epitope. Esp. it contains no epitopes from other M. catarrhalis **antigens**.

USE - Ag and Ab are useful, in standard immunoassays, for detecting the other binding partner, i.e. for diagnosis of M. catarrhalis infections (partic. **otitis media**).

Ab can be used to induce tolerance (passive immunisation) while Ag are used as active ingredients in protective vaccines. Ab, partic. those which recognise the 30 kD and HMW OMP, are reactive with a wide range of pathogen subtypes and isolates. Ab can also be used for purificn. of Ag. (I) can be used to express recombinant Ag, and nucleic acid fragments can also be used as hybridisation probes or PCR primers for detection of M. catarrhali

Dwg.0/5

ABEQ EP 612250 B UPAB: 960829
An **antigen** composition comprising a purified protein or peptide **antigen** incorporating an epitope that is immunologically cross-reactive with M. catarrhalis 30 kD or HMWP OMP.
Dwg.0/5

ABEQ US 5552146 A UPAB: 961011
An **antigen** composition comprising an Moraxella catarrhalis outer membrane **antigen** selected from the group consisting of M. catarrhalis outer membrane **antigens** immunologically reactive with monoclonal antibody 10F3 (ATCC HB 11092) or 17C7 (ATCC 11093), wherein said **antigen** is purified free of other M. catarrhalis outer membrane **antigens**.
Dwg.0/3

ABEQ US 5599693 A UPAB: 970313
Preparing an **antigen** compsn. comprises:
(a) selecting cells expressing a Moraxella catarrhalis outer membrane protein or peptide **antigen** having an epitope that binds to a monoclonal antibody selected from the group consisting of 8B6 (ATCC HB 11091), 10F3 (ATCC HB 11092) and 17C7 (ATCC HB 11093);
(b) culturing the selected cells under conditions effective for expression of the **antigen**; and
(c) collecting the **antigen** to prepare the compsn.
Dwg.0/3

L8 ANSWER 36 OF 58 TOXLIT
AN 1994:22750 TOXLIT
DN CA-120-002261F
TI Cloning and expression of **high** molecular **weight** surface proteins of non-typeable Haemophilus.
AU Barenkamp SJ
SO (1993). PCT Int. Appl. PATENT NO. 93 19090 09/30/93.
CY United States
DT Patent
FS CA
LA English
OS CA 120:2261
EM 199405
AB The genes for **high** mol. **wt**. surface proteins HMW1 and 2 of **H. influenzae** are cloned and sequenced. The amino acid sequences of HMW1 and 2 derived from the genes had high homol. with that of the filamentous hemagglutinin of Bordetella pertussia. The HMW1 and 2 are useful for prepn. of protective **antigens** against nontypeable Haemophilus-assocd. diseases such as otitis, sinusitis, bronchitis, etc., and as carrier for the protective Hib carrier polysaccharides in a conjugate vaccine against meningitis. The genes for the **high** mol. **wt**. surface proteins were cloned from a genomic library of **H. influenzae** constructed on

lambdaEMBL3 by immunol. screening using an human antibody against the **high** mol. **wt.** surface proteins. Also shown was the adherence of the HMW1 and 2 on the Chang epithelial cells. HMW3 and 4 were also cloned and partially sequenced.

L8 ANSWER 37 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 93346827 EMBASE
DN 1993346827
TI Formation of the K30 (group I) capsule in Escherichia coli O9:K30 does not require attachment to lipopolysaccharide lipid A-core.
AU MacLachlan P.R.; Keenleyside W.J.; Dodgson C.; Whitfield C.
CS Department of Microbiology, University of Guelph,Guelph, Ont. N1G 2W1, Canada
SO Journal of Bacteriology, (1993) 175/23 (7515-7522).
ISSN: 0021-9193 CODEN: JOBAAY
CY United States
DT Journal; Article
FS 004 Microbiology
LA English
SL English
AB Escherichia coli K **antigens** (capsular polysaccharides) are divided into two broad classes, designated groups I and II, on the basis of a number of chemical, physical, and genetic criteria. Group I K **antigens** can be further subdivided on the basis of the absence (group IA) or presence (group IB) of amino sugars in the repeating unit of the K **antigen**. One criterion proposed for inclusion in group I is covalent linkage of the capsular polysaccharide to the lipid A-core of lipopolysaccharide (LPS). E. coli O9:K30 is a strain with a representative group IA K **antigen**. This organism synthesizes an LPS- associated low-molecular-weight form of K30 **antigen** which is called K(LPS). To determine the involvement of LPS lipid A-core in expression of the K30 capsular polysaccharide, E. coli K30/K-12 hybrid strains were constructed with mutations in the E. coli K-12 rfa locus, responsible for the biosynthesis of the LPS core oligosaccharide. These strains lack K(LPS), indicating that a full-length core is required for K(LPS) expression. However, formation of a K30 capsule was unaffected by rfa defects, indicating that attachment to lipid A-core is not an obligatory step for either export of **high**-molecular-**weight** capsular polysaccharide or maintenance of the capsular structure on the cell surface. Silver-stained tricine-sodium dodecyl sulfate-polyacrylamide gel electrophoresis profiles of lipopolysaccharides from other E. coli K serotypes showed that all strains with group IB K **antigens** expressed some K(LPS). In contrast, some strains with group IA K **antigens** appear to lack K(LPS). Consequently, although association of group I K **antigens** with lipid A-core is common, it is not a universal marker for inclusion in group I.

Searcher : Shears 308-4994

DUPLICATE 18

L8 ANSWER 38 OF 58 MEDLINE
AN 94041638 MEDLINE
DN 94041638
TI Outer membrane protein binding sites of complement component 3 during opsonization of **Haemophilus influenzae**.
AU Hetherington S V; Patrick C C; Hansen E J
CS Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee 38101-0318..
NC P30 OCA 21765 (NCRR)
2 SO7 RR 05584-24
SO INFECTION AND IMMUNITY, (1993 Dec) 61 (12) 5157-63.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-J03381; GENBANK-J03359; GENBANK-M19391
EM 199402
AB Complement component 3 (C3) binding to **Haemophilus influenzae** type b (Hib) is an important step in host defense against invasive disease, but the details of this process remain poorly understood. We have shown that the P1 and P2 outer membrane proteins (OMPs) serve as binding sites for C3 on serum-opsonized Hib. Whole-cell lysates of opsonized Hib were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and the resolved proteins were transferred to nitrocellulose. Immunoblot analysis with monoclonal antibodies (MAbs) to the 49-kDa P1 and 39-kDa P2 OMPs demonstrated **high**-molecular-**weight** bands that were not present when the bacteria were opsonized with heat-inactivated or methylamine-treated serum. Immunoblot analysis with MAbs to the 98- or 16-kDa (P6) OMPs did not reveal additional bands. An unencapsulated Hib mutant still lacked C3 bound to the 98-kDa or P6 OMP, indicating that the absence of C3 binding to these proteins was not the result of epitope masking by the capsule. Studies with MAbs to C3 fragments confirmed that the anti-P1- and anti-P2-reactive bands were C3 fragments bound to these OMPs. The molecular weights of proteins reactive to anti-OMP and anti-C3 antibodies indicated that multiple C3 fragments may be bound to P1 or that C3 may be bound to P2 multimers. Finally, the presence of other anti-C3-reactive proteins indicated that several other proteins serve as C3 targets during the opsonization of Hib.

L8 ANSWER 39 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1993:501112 BIOSIS
DN PREV199396125119
TI Characterisation of Plesiomonas shigelloides strains that share type-specific **antigen** with Shigella flexneri 6 and common group 1 **antigen** with Shigella flexneri spp. and Shigella

dysenteriae 1.

AU Albert, M. J. (1); Ansaruzzaman, M.; Qadri, F.; Hossain, A.; Kibriya, A. K. M. G.; Haider, K.; Nahar, S.; Faruque, S. M.; Alam, A. N.

CS (1) Lab. Sci. Div., ICDDR, B, G.P.O. Box 128, Dhaka 1000 Bangladesh

SO Journal of Medical Microbiology, (1993) Vol. 39, No. 3, pp. 211-217. ISSN: 0022-2615.

DT Article

LA English

AB Three strains of Plesiomonas shigelloides isolated from patients with diarrhoea were agglutinated with Shigella flexneri 6 antiserum in slide and tube tests. All the strains were also agglutinated with a monoclonal antibody to the common group 1 **antigen** shared between S. flexneri serotypes and S. dysenteriae type 1. Further studies with one strain also showed sharing of antigenicity in an enzyme-linked immunosorbent assay. The results suggest that the strains share type-specific **antigen** with S. flexneri 6 and the common group 1 **antigen** with S. flexneri serotypes and S. dysenteriae 1. The sharing of **antigens** may have implications for cross-protection. One strain adhered to HEp-2 cell monolayers. None of the strains contained **high** mol. **wt** plasmids and there was no sequence homology with the invasiveness plasmid of Shigella spp. in DNA probe hybridization. They were susceptible to the commonly used antibiotics. However, they possessed four other virulence-associated properties of Shigella spp. that included Congo-red binding, hydrophobicity, toxicity to HeLa cells and Hep-2 cell invasiveness (although they gave negative results in the Sereny test for invasiveness). These data suggest that the three unique strains might be considered pathogenic. Studies in animal models and human volunteers would be necessary to establish their pathogenic potential.

L8 ANSWER 40 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 19

AN 1993:292934 BIOSIS

DN PREV199345011059

TI The ANWJ blood group **antigen Haemophilus influenzae** receptor resides on a **high**-molecular-**weight** protein expressed by CD44 transfectants.

AU Telen, M. J.; Rao, N.; Udani, M.; Liao, H.-X.; Haynes, B. F.

CS Duke Univ. Med. Center, Durham, NC USA

SO Clinical Research, (1993) Vol. 41, No. 2, pp. 161A. Meeting Info.: Joint Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Clinical Research Washington, DC, USA April 30-May 3, 1993 ISSN: 0009-9279.

DT Conference

LA English

L8 ANSWER 41 OF 58 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 92-058283 [08] WPIDS
TI New immunogenic conjugate - comprises **antigen** bound to filamentous haemagglutinin of Bordetella pertussis, used as carrier for conjugate vaccines.
DC B04 D16
IN COWELL, J L; DICK, W E; KIMURA, A
PA (AMCY) AMERICAN CYANAMID CO
CYC 18
PI EP 471177 A 920219 (9208)*
R: AT BE CH DE ES FR GB GR IT LI NL SE
NO 9103130 A 920214 (9216)
AU 9181789 A 920220 (9218)
CA 2048917 A 920214 (9218)
FI 9103820 A 920214 (9219)
JP 04230634 A 920819 (9241) 7 pp
EP 471177 A3 930224 (9348)
AU 649700 B 940602 (9427)
EP 471177 B1 951004 (9544) EN 9 pp
R: AT BE CH DE DK ES FR GB GR IT LI NL SE
DE 69113564 E 951109 (9550)
ADT EP 471177 A EP 91-110919 910702; FI 9103820 A FI 91-3820 910812; JP 04230634 A JP 91-222392 910808; EP 471177 A3 EP 91-110919 910702; AU 649700 B AU 91-81789 910812; EP 471177 B1 EP 91-110919 910702; DE 69113564 E DE 91-613564 910702, EP 91-110919 910702
FDT AU 649700 B Previous Publ. AU 9181789; DE 69113564 E Based on EP 471177
PRAI US 90-565161 900813
AN 92-058283 [08] WPIDS
AB EP 471177 A UPAB: 940120
An immunogenic conjugate comprises an **antigen** coupled to a filamentons haemogglutinin (FHA) of Bordetella pertussis or its immunologically active fragment, or to an immunologically cross-reactive mutant FHA of B pertussis or its portion.

Also claimed is an immuniogenic conjugate comprising polyribosylribitolphosphate (PRRP) coupled to a FHA of B pertussis or its immunologically active portion, or to an immunologically cross-reactive mutant of FHA of B pertussis or its portion. The anigen is a carbohydrate e.g. a bacterial capsular oligosaccharide or polysaccharide or their fragments, esp. from H. influence, Streptococcus pneumoniae, Neiserria meningitidis, Klebsiella pneuamoniae, Pseudomonas aruginosa and Staphylococcus aureus, and is pref. PRRP.

USE/ADVANTAGE - The conjugates are used as a vaccine, and for treatment and prophylaxis of e.g. AIDs and post-exposive conditions. FHA acts as a carrier for **antigens**, e.g. bacteria, viruses and cellular microcomponents, as it is nontoxic, has a relatively **high** mol. **wt.** and after conjugation with **antigens** retains both T- and B-cell epitopes. FHA may also

help to protect against marginally or non-immunogenic **antigens** when they are conjugated to FHA. When the **antigen** is (PRRP) of **Haemophilus influenzae** type P the vaccine is against meningitis. Admin. is intradermal, transdermal (e.g. by slow release polymers) intransmuscular, intraperitoneal, intravenous, subcutaneous, oral and intranasal. @(8pp Dwg.No.0/0

ABEQ EP 471177 A UPAB: 940120

An immunogenic conjugate comprises an **antigen** coupled to a filamentons haemogglutinin (FHA) of Bordetella pertussis or its immunologically active fragment, or to an immunologically cross-reactive mutant FHA of B pertussis or its portion.

Also claimed is an immuniogenic conjugate comprising polyribosylribitolphosphate (PRRP) coupled to a FHA of B pertussis or its immunologically active portion, or to an immunologically cross-reactive mutant of FHA of B pertussis or its portion. The anigen is a carbohydrate e.g. a bacterial capsular oligosaccharide or polysaccharide or their fragments, esp. from H. influence, Streptococcus pneumoniae, Neiserria meningitidis, Klebsiella pneuamoniae, Pseudomonas aruginosa and Staphylococcus aureus, and is pref. PRRP.

USE/ADVANTAGE - The conjugates are used as a vaccine, and for treatment and prophylaxis of e.g. AIDs and post-exposive conditions. FHA acts as a carrier for **antigens**, e.g. bacteria, viruses and cellular microcomponents, as it is nontoxic, has a relatively **high** mol. **wt.** and after conjugation with **antigens** retains both T- and B-cell epitopes. FHA may also help to protect against marginally or non-immunogenic **antigens** when they are conjugated to FHA. When the **antigen** is (PRRP) of **Haemophilus influenzae** type P the vaccine is against meningitis. Admin. is intradermal, transdermal (e.g. by slow release polymers) intransmuscular, intraperitoneal, intravenous, subcutaneous, oral and intranasal. @(8pp Dwg.No.0/0

ABEQ EP 471177 B UPAB: 951109

An immunogenic conjugate, comprising an **antigen** coupled to a filamentous hemagglutinin of Bordetella pertussis or an immunologically active portion thereof, or to an immunologically cross-reactive mutant filamentous hemagglutinin of Bordetella pertussis or portion thereof.

Dwg.0/0

DUPLICATE 20

L8 ANSWER 42 OF 58 MEDLINE

AN 92268652 MEDLINE

DN 92268652

TI Outer membrane proteins and lipopolysaccharides of nontypeable **Haemophilus influenzae**.

AU Barenkamp S J

CS Edward Mallinckrodt Department of Pediatrics, Washington University

Searcher : Shears 308-4994

School of Medicine, St. Louis, Missouri..
NC AI-21707 (NIAID)
SO JOURNAL OF INFECTIOUS DISEASES, (1992 Jun) 165 Suppl 1 S181-4. Ref: 12
Journal code: IH3. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199208
AB Several outer-membrane proteins of nontypeable **Haemophilus influenzae** are potential vaccine candidates: P2 and P6 elicit antibodies that are bactericidal and protective in experimental models of infection. Other proteins are being investigated. A group of surface-exposed **high**-molecular-**weight** proteins that are major targets of antibody in human convalescent sera were identified. Monoclonal antibodies to the **high**-molecular-**weight** proteins of a prototype strain recognized two distinct but related proteins and were bactericidal for the prototype strain and other strains that shared the epitope recognized by the monoclonals. Genes encoding the two proteins in the prototype strain recognized by the monoclonals were cloned and sequenced. The sequences were distinct but related, and the derived amino acid sequences had sequence similarity to that of filamentous hemagglutinin of Bordetella pertussis, an important adherence factor and protective **antigen**.

L8 ANSWER 43 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1992:316953 BIOSIS
DN BR43:17678
TI **HIGH MOLECULAR WEIGHT HMW**
PROTEINS OF NONTYPABLE **HAEMOPHILUS-INFLUENZAE**
NTHI MEDIATE ATTACHMENT TO HUMAN EPITHELIAL CELLS.
AU ST GEME J W III; FALKOW S; BARENKAMP S J
CS STANFORD UNIV. SCH. MED., DEP. MICROBIOL. IMMUNOL., STANFORD, CALIF.
SO MEETING OF THE AMERICAN PEDIATRIC SOCIETY AND THE SOCIETY FOR PEDIATRIC RESEARCH, BALTIMORE, MARYLAND, USA, MAY 4-7, 1992. PEDIATR RES. (1992) 31 (4 PART 2), 179A.
CODEN: PEREBL. ISSN: 0031-3998.
DT Conference
FS BR; OLD
LA English

L8 ANSWER 44 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 21
AN 1992:382914 BIOSIS
DN BR43:49864
TI A **HIGH**-MOLECULAR-**WEIGHT** OUTER MEMBRANE PROTEIN

THAT IS A POTENTIAL TARGET FOR PROTECTIVE IMMUNITY TO TYPE B AND UNTYPABLE **HAEMOPHILUS-INFLUENZAE**.

AU THOMAS W R; FLACK F S; CALLOW M G; CHUA K-Y

CS WEST. AUST. RES. INST. CHILD HEALTH, GPO BOX D184, PERTH 6001, WEST. AUST., AUST.

SO MEETING ON EPIDEMIOLOGY, PATHOGENESIS, AND PREVENTION OF HAEMOPHILUS INFLUENZAE DISEASE, VELDHOVEN, NETHERLANDS, SEPTEMBER 24-28, 1990. J INFECT DIS. (1992) 165 (SUPPL 1), S75-S76.
CODEN: JIDIAQ. ISSN: 0022-1899.

DT Conference

FS BR; OLD

LA English

L8 ANSWER 45 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

AN 92175681 EMBASE

DN 1992175681

TI Outer membrane proteins and lipopolysaccharides of nontypeable **Haemophilus influenzae**.

AU Barenkamp S.J.

CS Department of Pediatrics, St. Louis University, School of Medicine, 1465 S. Grand Blvd.,St. Louis, MO 63104, United States

SO Journal of Infectious Diseases, (1992) 165/SUPPL. 1 (S181-S184).
ISSN: 0022-1899 CODEN: JIDIAQ

CY United States

DT Journal; General Review

FS 004 Microbiology
007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation

LA English

SL English

AB Several outer membrane proteins of nontypeable **Haemophilus influenzae** are potential vaccine candidates: P2 and P6 elicit antibodies that are bactericidal and protective in experimental models of infection. Other proteins are being investigated. A group of surface-exposed **high**-molecular-**weight** proteins that are major targets of antibody in human convalescent sera were identified. Monoclonal antibodies to the **high**-molecular-**weight** proteins of a prototype strain recognized two distinct but related proteins and were bactericidal for the prototype strain and other strains that shared the epitope recognized by the monoclonals. Genes encoding the two proteins in the prototype strain recognized by the monoclonals were cloned and sequenced. The sequences were distinct but related, and the derived amino acid sequences had sequence similarity to that of filamentous hemagglutinin of Bordetella pertussis, an important adherence factor and protective **antigen**.

L8 ANSWER 46 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

AN 92175647 EMBASE

DN 1992175647
TI A **high**-molecular-**weight** outer membrane protein that is a potential target for protective immunity to type b and untypeable **Haemophilus influenzae**.
AU Thomas W.R.; Flack F.S.; Callow M.G.; Chua K.Y.
CS WA Res. Inst. for Child Health, GPO Box D184,Perth, WA 6001, Australia
SO Journal of Infectious Diseases, (1992) 165/SUPPL. 1 (S75-S76). ISSN: 0022-1899 CODEN: JIDIAQ
CY United States
DT Journal; Article
FS 004 Microbiology
007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
LA English

DUPLICATE 22

L8 ANSWER 47 OF 58 MEDLINE
AN 90256277 MEDLINE
DN 90256277
TI Expression in Escherichia coli of a **high**-molecular-**weight** protective surface **antigen** found in nontypeable and type b **Haemophilus influenzae**.
AU Thomas W R; Callow M G; Dilworth R J; Audesho A A
CS Clinical Immunology Research Unit, Princess Margaret Hospital, Subiaco, Western Australia..
SO INFECTION AND IMMUNITY, (1990 Jun) 58 (6) 1909-13. Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199008
AB An Escherichia coli clone producing a **high**-molecular-**weight** surface **antigen** of **Haemophilus influenzae** type b (Hib) was isolated from a library of Hib DNA fragments cloned as lysogens in a lambda replacement vector. The **antigen** is found in sarcosyl-insoluble outer membrane protein preparations and was produced by all 36 **H. influenzae** isolates tested. Absorption studies indicated that the **antigen** is a surface determinant on all isolates tested. Antibodies to the **antigen** (D15) were found in eight of nine convalescent-phase sera from children with invasive Hib infection. Affinity-purified antibodies prepared against the cloned **antigen** gave protection against the development of bacteremia in a rat pup model.

L8 ANSWER 48 OF 58 MEDLINE
AN 86113570 MEDLINE
DN 86113570

TI Inhibition of attachment of Streptococcus pneumoniae and **Haemophilus influenzae** by human milk and receptor oligosaccharides.
AU Andersson B; Porras O; Hanson L A; Lagergard T; Svanborg-Eden C
SO JOURNAL OF INFECTIOUS DISEASES, (1986 Feb) 153 (2) 232-7. Journal code: IH3. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198605
AB Human milk inhibited the attachment of Streptococcus pneumoniae and **Haemophilus influenzae** to human pharyngeal or buccal epithelial cells. Infant formulas and cow and buffalo milk showed a lower inhibitory activity against pneumococci and enhanced the adhesion of **H. influenzae**. The antiadhesive effect against S. pneumoniae was found in both the high- and the low-molecular-weight fractions of milk. The inhibitory activity in the **high**-molecular-**weight** fraction was independent of specific antibody content; it was present after immunoadsorption and in the milk from IgA-deficient women. The inhibitory activity in the low-molecular-weight fraction was in part explained by the content of oligosaccharides corresponding to the carbohydrate moieties of the neolactoseries of glycolipids, which have previously been shown to act as receptors for attaching pneumococci. The antiadhesive activity against **H. influenzae** was restricted to the **high**-molecular-**weight** fraction of the milk and was unaffected by immunoadsorption. Milk may protect against otitis by reducing colonization.

L8 ANSWER 49 OF 58 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 86-07882 BIOTECHDS
TI Cloning and expression of a gene encoding an immunogenic, extracellular protein of **Haemophilus influenzae** type b in Escherichia coli; application to vaccine production (conference abstract)
AU Gonzales F R; Norgard M V; Kupersztoch J M; Hansen E J
LO University of Texas Health Science Center at Dallas, Dallas, TX 75235, U.S.A.
SO Abstr.Annu.Meet.Am.Soc.Microbiol.; (1986) 86 Meet., 90, D-145
DT Journal
LA English
AN 86-07882 BIOTECHDS
AB **Haemophilus influenzae** type b (Hib) synthesizes a **high** mol.**wt**. (100,000) protein which is immunogenic in human infants with Hib meningitis. To facilitate genetic analysis of the 100K protein, genomic libraries containing Hib DNA were constructed in Escherichia coli HB101 using the

cloning vehicle pBR322. More than 12,000 recombinant clones were screened in a colony blot-RIA using a murine monoclonal antibody directed against the Hib 100K protein. 10 Clones reactive with this monoclonal antibody contained a hybrid plasmid bearing an insert of approximately 13.5-kb of Hib DNA. Each recombinant clone synthesized a protein **antigen** with an apparent mol.wt. identical to that of the native Hib protein. (0 ref)

L8 ANSWER 50 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 85147697 EMBASE
DN 1985147697
TI Composition and antigenic activity of the oligosaccharide moiety of **Haemophilus influenzae** type b lipooligosaccharide.
AU Inzana T.J.; Seifert Jr. W.E.; Williams R.P.
CS Department of Microbiology and Immunology, Baylor College of Medicine, Houston, TX 77030, United States
SO Infection and Immunity, (1985) 48/2 (324-330).
CODEN: INFIBR
CY United States
DT Journal
FS 026 Immunology, Serology and Transplantation
004 Microbiology
LA English
AB The oligosaccharide moiety of the lipooligosaccharide of **Haemophilus influenzae** type b strain Eag was isolated from the lipid component by mild acid hydrolysis and purified by gel filtration. Fast atom bombardment-mass spectrometry indicated that the lipid-free oligosaccharide had a basic molecular weight of 1,768; polysaccharides comparable to **high -molecular-weight** O side chains were not found. Glucose, galactose, galactosamine, heptose, 3-deoxy-D-manno-2-octulosonic acid (KDO), ethanolamine, and phosphate were identified in the lipid-free oligosaccharide by colorimetric assays, gel chromatography-mass spectrometry, or an amino acid analyzer. The presence of KDO was not clearly established by a thiobarbituric acid assay or by growth inhibition by a diazaborine derivative thought to block KDO synthesis. However, the semicarbizide assay and gas chromatography-mass spectrometry confirmed the presence of KDO. Lectin precipitation by Eag lipooligosaccharide in gels indicated that .beta.-D-galactose was present and that some of this monosaccharide was a terminal, nonreducing residue linked to N-acetyl-D-galactosamine. The lipid-free oligosaccharide was antigenic and completely inhibited lipooligosaccharide antibody (predominantly immunoglobulin G [IgG] and IgM) in an enzyme-linked immunosorbent assay, whereas the solubilized lipid A moiety did not. **H. influenzae** type b lipid-free oligosaccharide differed from core oligosaccharide of Salmonella lipooligosaccharide by the presence of galactosamine and a smaller percentage of heptose and KDO.

Searcher : Shears 308-4994

L8 ANSWER 51 OF 58 MEDLINE DUPLICATE 23
AN 85078580 MEDLINE
DN 85078580
TI A minor **high**-molecular-**weight** outer membrane protein of **Haemophilus influenzae** type b is a protective **antigen**.
AU Kimura A; Gulig P A; McCracken G H Jr; Loftus T A; Hansen E J
NC AI-17621 (NIAID)
AI-17012 (NIAID)
SO INFECTION AND IMMUNITY, (1985 Jan) 47 (1) 253-9.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198504
AB Cell surface-exposed antigenic determinants of several **high**-molecular-**weight** outer membrane proteins of **Haemophilus influenzae** type b (Hib) have been shown to be consistently immunogenic in human infants convalescing from Hib meningitis. A monoclonal antibody (mab), 6G12, directed against one of these cell surface-exposed outer membrane proteins that has an apparent molecular weight of 98,000 (98K) was identified by radioimmunoprecipitation analysis. Of 120 clinical isolates of Hib, 83 were found to possess antigenic determinants which reacted with mab 6G12 in a colony blot-radioimmunoassay procedure, indicating that the antigenic determinant recognized by mab 6G12 is present in the majority of Hib strains. A different radioimmunoassay, which uses whole Hib cells as **antigen**, confirmed that strains reactive with mab 6G12 in the colony blot-radioimmunoassay procedure possessed a cell surface-exposed and antibody-accessible antigenic determinant recognized by this mab. Hib strains which did not react with mab 6G12 were found to lack a 98K protein. Passive immunization with mab 6G12 reduced the level of bacteremia that developed in infant rats challenged with the homologous Hib strain against which this mab was raised. In contrast, no protection was observed when the challenge strain was one which lacks the antigenic determinant recognized by mab 6G12. Radioimmunoprecipitation analysis of sera from human infants convalescing from Hib meningitis detected an antibody response directed against the 98K protein. The protection against experimental Hib disease provided by antibody to the 98K protein, the immunogenicity of this protein in human infants, and its presence in a majority of Hib strains indicate that the 98K outer membrane protein may have potential for vaccine development.

L8 ANSWER 52 OF 58 MEDLINE
AN 85071741 MEDLINE

DN 85071741
TI Complement in chronic secretory **otitis media**. C3 breakdown and C3 splitting activity.
AU Meri S; Lehtinen T; Palva T
SO ARCHIVES OF OTOLARYNGOLOGY, (1984 Dec) 110 (12) 774-8. Journal code: 860. ISSN: 0003-9977.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198503
AB Occurrence of in vivo C3 breakdown and in vitro C3 splitting activity was studied in serum and middle-ear effusion (MEE) samples from 30 children with chronic secretory **otitis media** (SOM). The MEE showed strongly elevated levels of both low- and **high**-molecular-**weight** C3 breakdown products, along with decreased factor B, C4, and C3 levels. Total hemolytic complement component activity was virtually absent from MEE. The MEE fluids were found to contain C3 splitting factors as demonstrated by their high capacity to convert C3 in vitro from fresh normal human serum. This activity was not inhibited by the classic complement pathway inhibitor, 0.01M ethylene glycol tetra-acetic acid with 0.005M magnesium chloride. The results suggest that a strong local complement activation has taken place and that the factors responsible are present in the MEE of patients with SOM.

L8 ANSWER 53 OF 58 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1984:100652 BIOSIS
DN BR27:17144
TI IDENTIFICATION OF AN IMMUNOGENIC **HIGH** MOLECULAR **WEIGHT** OUTER MEMBRANE PROTEIN OF **HAEMOPHILUS-INFLUENZAE** TYPE B AS A PROTECTIVE **ANTIGEN**.
AU KIMURA A; MCCRACKEN G H JR; GULIG P A; LOFTUS T A; HANSEN E J
CS UNIV. TEX. HEALTH SCI. CENT., DALLAS, TEX.
SO 84TH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, ST. LOUIS, MO., USA, MAR. 4-9, 1984. ABSTR ANNU MEET AM SOC MICROBIOL. (1984) 84 (0), ABSTRACT B99.
CODEN: ASMACK. ISSN: 0094-8519.
DT Conference
FS BR; OLD
LA English

L8 ANSWER 54 OF 58 MEDLINE
AN 77251039 MEDLINE
DN 77251039
TI Immunogenicity in weanling rabbits of a polyribophosphate complex from **Haemophilus influenzae** type b.
AU Anderson P; Smith D H

SO JOURNAL OF INFECTIOUS DISEASES, (1977 Aug) 136 Suppl S63-70.
Journal code: IH3. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197712
AB Polyribophosphate (PRP), the capsular polysaccharide of **Haemophilus influenzae** type b, is more effectively immunogenic when it is associated with the bacterium than when it is in the purified form that is being tested as a vaccine for humans. In an effort to analyze this difference, we isolated from **H**
. **influenzae** type b a **high**-molecular-**weight**, soluble complex, in which PRP appears to be combined with protein (about 7% protein). The pyrogenicity and limulus lysate gelation activity of the complex suggest that a small amount of lipopolysaccharide also is present. The protein was resolved into five polypeptides by electrophoresis in polyacrylamide gel containing sodium dodecyl sulfate. In weanling rabbits, which do not respond to purified PRP, the complex induces high titers of antibody of PRP, in an anamnestic pattern. Bactericidal antibody to other bacterial components was also elicited. Equilibrium density gradient centrifugation of the complex indicated that most of the immunogenicity of PRP resides in the least dense fractions, which are high in protein, low in polysaccharide, and active in the limulus lysate test; denser fractions that react strongly with limulus lysate but are poor in protein were much less immunogenic.

L8 ANSWER 55 OF 58 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 78171986 EMBASE
DN 1978171986
TI Immunogenicity in weanling rabbits of a polyribophosphate complex from **Haemophilus influenzae** type b.
AU Anderson P.; Smith D.H.
CS Infect. Dis. Div., Child Hosp. Med. Cent., Boston, Mass., United States
SO Journal of Infectious Diseases, (1977) 136/2 Suppl. (S63-S70).
CODEN: JIDIAQ
CY United States
DT Journal
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
AB Polyribophosphate (PRP), the capsular polysaccharide of **Haemophilus influenzae** type b, is more effectively immunogenic when it is associated with the bacterium than when it is in the purified form that is being tested as a vaccine for humans. In an effort to analyze this difference, we isolated from **H**
. **influenzae** type b a **high**-molecular-

weight, soluble complex, in which PRP appears to be combined with protein (about 7% protein). The pyrogenicity and limulus lysate gelation activity of the complex suggest that a small amount of lipopolysaccharide also is present. The protein was resolved into five polypeptides by electrophoresis in polyacrylamide gel containing sodium dodecyl sulfate. In weanling rabbits, which do not respond to purified PRP, the complex induces high titers of antibody to PRP, in an anamnestic pattern. Bactericidal antibody to other bacterial components was also elicited. Equilibrium density gradient centrifugation of the complex indicated that most of the immunogenicity of PRP resides in the least dense fractions, which are high in protein, low in polysaccharide, and active in the limulus lysate test; denser fractions that react strongly with limulus lysate but are poor in protein were much less immunogenic.

L8 ANSWER 56 OF 58 MEDLINE DUPLICATE 24
AN 76266429 MEDLINE
DN 76266429
TI [Experimental studies on the reaction of the immunological system during chronic **otitis media** and about the course of this disease (author's transl)].
Experimentelle Untersuchungen zum Verhalten des Immunsystems bei der chronischen Mittelohreiterung und zum Verlauf dieses Krankheitsbildes.
AU Kastenbauer E R; Hochstrasser K
SO LARYNGOLOGIE, RHINOLOGIE, OTOLOGIE, (1976 Jan) 55 (1) 36-42.
Journal code: L1R. ISSN: 0340-1588.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 197612
AB During chronic **otitis media** intact immunoglobulins are split due to the proteolytic activity of extracellular bacterial proteinases into fragments of different molecular weight. The most malignant bacterial proteinases are the proteinases of pseudomonas aeruginosa (pyrocyanea). These proteinases can only be inhibited by alpha-2-macroblobulin of human blood serum. Because of its **high** molecular **weight** we find this inhibitor only in a very low concentration in the middle ear secretion. The destruction of the immunoglobulins is certainly one of the factors of weakening the immunological system in the middle ear. The inhibitory system with alpha-1-antitrypsin, inter-alpha-trypsin inhibitor and alpha-1-antichymotrypsin is unable to inhibit these bacterial proteinases of pseudomonas aeruginosa. The only possibility to get a high concentration of alpha-2-macroglobulin in the middle ear secretion is the liberation of this inhibitory by injuring blood vessels during a tympanoplasty. By this procedure the proteinases of pseudomonas aeruginosa with

maximum activity at pH 7.8 and with a high proteolytic activity are almost completely inhibited. By blocking these proteinases combined with an appropriate antibiotic therapy and with the reconstruction of the destroyed parts of the middle ear by a tympanoplasty we can produce a preponderance of the immunological system as compared with the proteolytic activity of the proteinases. This high proteolytic activity can be a cause of the destruction of the small processes of the ossicular bones, especially of the lenticular process of incus. In order to demonstrate that there are proteolytic splitting processes of intact immunoglobulins, a quantitative analysis of the immunoglbulins IgG, IgA and IgM was done pre- and postoperatively. By these studies we found postoperatively a much higher level of intact immunoglobulins, particulary in cases of chronic **otitis media** associated with cholesteatoma. The blocking of the proteinases and the increase of the level of intact immunoglobulins combined with the reconstruction of physiological conditions in the chronically inflamed middle ear by a tympanoplasty lead to a stabilsation of the immunological and inhibitory system and create the prerequisites for a healing process in chronic **otitis media**. It is the purpose of further studies to learn about the capability of the split-products of the immunoglobulines to attach and to absorb **antigens** and toxins during a chronic inflammation in the middle ear.

L8 ANSWER 57 OF 58 MEDLINE DUPLICATE 25
AN 75155226 MEDLINE
DN 75155226
TI [Enzymatic and immunological inflammatory reactions in the middle ear (author's transl)].
Enzymatische und immunologische Entzundungsreaktionen im Mittelohr.
AU Kastenbauer E R
SO LARYNGOLOGIE, RHINOLOGIE, OTOLOGIE, (1975 Mar) 54 (3) 177-82.
Journal code: L1R. ISSN: 0340-1588.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 197509
AB During chronic **otitis media** intact immunoglobulins are split by extracellular bacterial proteinases into fragments of different molecular weight, The most malignant extracellular proteinases with the greatest proteolytic activity against intact immunoglobulins are the bacterial proteinases of Pseudomonas aeruginosa. These proteinases cannot be inhibited by the other serum proteinase-inhibitor except for Alpha-2-Macroglobulin of the human blood serum. This inhibitor has a very **high** molecular **weight**, so that we cannot find it in a higher concentration in the middle-ear-secretory. We can liberate this inhibitor by injuring the blood vessels during a tympanoplasty. In

this way we get an inhibitory effect against these proteinases and combined with an appropriate antibiotic therapy we can cure a chronic **otitis MEDIA**. In order to demonstrate that there are immunological reactions in the middle ear against homografted ossicles, various transplantation with homologous ossicles have been performed between two inbreeding rat strains. After sensitisation of the host animals against **antigens** of the donor animals with skin grafts a reliable histologic infiltration with plasma cells and lymphocytes and the rejection of the graft could be insured. After a simple homologous transplantation without sensitisation, these rejection reactions occurr only rarely and in a diminished form. Cialit storage of middle ear ossicles decreases the solubility of the contained proteins and this in turn diminishes the antigenicity, the amount the **antigens**, or it retards their liberation. It is for these reasons that Cialit-stored ossicles are more slowly transformed, and there are less inflammatory reactions and adhesions than with untreated ones. The osteogenetic capability of the ossicles is not affected by the Cialit storage.

L8 ANSWER 58 OF 58 CONFSCI COPYRIGHT 1999 CSA
AN 84:494 CONFSCI
DN 84006161
TI Identification of an immunogenic, **high**-molecular-**weight** outer membrane protein of **Haemophilus influenzae** type b as a protective **antigen**
AU Kimura, A.; McCracken, G.H.,Jr.; Gulig, P.A.; Loftus, T.A.; Hansen, E.J.
CS Univ. Texas Health Sci. Cent., Dallas
SO Abstracts available: American Society for Microbiology, Publications Department, 1913 I St. NW, Washington, DC 20006, USA, Paper No. B99.
Meeting Info.: 841 0195: American Society for Microbiology 84th Annual Meeting (8410195). St. Louis, MO (USA). 4-9 Mar 84. American Society for Microbiology (ASM).
DT Conference
FS DCCP
LA UNAVAILABLE

Claim 19

FILE 'REGISTRY' ENTERED AT 12:46:30 ON 25 MAR 1999
E ALUMINUM HYDROXIDE/CN 5
L9 332 SEA ABB=ON PLU=ON (ALUMINUM HYDROXIDE ? OR ALUMINUM PHOSPHATE ?)/CN

FILE 'CAPLUS' ENTERED AT 12:47:03 ON 25 MAR 1999
L10 17 SEA ABB=ON PLU=ON L1 AND (L9 OR (AL OR ALUMIN?)(W)(PHOS PHATE OR PO# OR HYDROXIDE OR OH) OR ALPO# OR ALOH)
L11 16 SEA ABB=ON PLU=ON L10 NOT L3

Searcher : Shears 308-4994

L11 ANSWER 1 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1998:106016 CAPLUS
DN 128:176969
TI The NucA protein of **Haemophilus influenzae** and its gene sequence and use as a vaccine
IN Zagursky, Robert John; Jones, Kevin Frederick; Ooi, Peggy
PA American Cyanamid Company, USA; Zagursky, Robert John; Jones, Kevin Frederick; Ooi, Peggy
SO PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9804703	A1	19980205	WO 97-US12790	19970723
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ZW				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2232975	AA	19980205	CA 97-2232975	19970723
	AU 9738077	A1	19980220	AU 97-38077	19970723
	EP 854925	A1	19980729	EP 97-935048	19970723
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 96-22619	19960726			
	US 96-687865	19960726			
	WO 97-US12790	19970723			

AB A protein from **H. influenzae** designated NucA is isolated and purified. The NucA protein has the amino acid sequence of 603 amino acid residues, or a biol. equiv. amino acid sequence. Amino acids 1-25 of NucA are the signal peptide, which is cleaved during processing of the mature protein. The NucA protein has a mol. wt. of .apprx.63 kDa as measured on a 12 % SDS-PAGE gel and possesses 5'-nucleotidase activity. The NucA protein is obtained by isolation and purifn. from the **H. influenzae** organism, by chem. synthesis, or by recombinant expression by an isolated and purified nucA DNA sequence which encodes the NucA protein. Such a DNA sequence hybridizes under std. high stringency Southern hybridization conditions with a DNA sequence encoding the NucA protein of **H. influenzae** having the amino acid sequence of the mature protein or a biol. equiv. amino acid sequence. The NucA protein is used to prep. a vaccine compn. which elicits a protective immune response in a mammalian host to protect the host against disease caused by **H. influenzae**

IT **7784-30-7, Aluminum phosphate**

21645-51-2, Aluminum hydroxide,
biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvant; NucA protein of **Haemophilus influenzae** and its gene sequence and use as a vaccine)

L11 ANSWER 2 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1998:55553 CAPLUS
DN 128:127079
TI Multivalent DTP-polio vaccines
IN Fahim, Raafat E. F.; Tan, Larry U. L.; Barreto, Luis; Thipphawong, John; Jackson, Gail E. D.
PA Connaught Laboratories Ltd., Can.; Fahim, Raafat E. F.; Tan, Larry U. L.; Barreto, Luis; Thipphawong, John; Jackson, Gail E. D.
SO PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9800167	A1	19980108	WO 97-CA472	19970702
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9732516	A1	19980121	AU 97-32516	19970702
PRAI US 96-672530		19960702		
WO 97-CA472		19970702		

AB A multi-component vaccine compn. is described comprising acellular pertussis vaccine components, diphtheria toxoid, tetanus toxoid, and inactivated poliovirus. The compn. also may contain a conjugate of a capsular polysaccharide of **Haemophilus influenzae** type b and tetanus toxoid or diphteria toxoid, which may be reconstituted from a lyophilized state by the other components of the vaccine. The administration of the multiple component vaccine results in no diminution in the immunogenicity of any component as a result of interference by other components of the vaccine.

IT **7784-30-7, Aluminum phosphate**
21645-51-2, Aluminum hydroxide,
biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn., immunogenicity, safety, and clin. effects of multivalent

vaccines against pertussis, diphtheria, tetanus, poliomyelitis, and **Haemophilus influenzae** infection in children in relation to)

L11 ANSWER 3 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1998:1387 CAPLUS
DN 128:74301
TI Monovalent pertussis vaccine and multivalent vaccines against hepatitis and Hib using pertactin
IN Slaoui, Moncef Mohamed; Stephenne, Jean
PA Smithkline Beecham Biologicals S.A., Belg.; Slaoui, Moncef Mohamed; Stephenne, Jean
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9746255	A2	19971211	WO 97-EP2956	19970529
WO 9746255	A3	19980108		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9731736	A1	19980105	AU 97-31736	19970529

PRAI GB 96-11501 19960603
WO 97-EP2956 19970529

AB Vaccine compns. comprising the 69K outer membrane protein of B. pertussis (pertactin) having 10-100 .mu.g of 69K per 0.5 mL dose are described for the treatment of whooping cough. Also described are combination vaccines comprising 10-100 .mu.g of 69K per 0.5 mL, esp. vaccines in which the 69K component is formulated with filamentous hemagglutinin (FHA) and pertussis toxoid (PT), optionally in combination with one or more other antigens such as hepatitis B surface antigen, **Haemophilus influenzae** b (Hib), injectable polio (IPV) and hepatitis A. Methods for prepg. the vaccines are described.

IT **7784-30-7**, **Aluminum phosphate**
21645-51-2, **Aluminum hydroxide**, uses
RL: MOA (Modifier or additive use); USES (Uses)
(monovalent pertussis vaccine and multivalent vaccines against hepatitis and **Haemophilus influenza** type b using pertactin)

L11 ANSWER 4 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1997:306965 CAPLUS
DN 127:3884
TI MF59 adjuvant enhances antibody responses of infant baboons immunized with **Haemophilus influenzae** type b and Neisseria meningitidis group C oligosaccharide-CRM197 conjugate vaccine
AU Granoff, Dan M.; McHugh, Yvonne E.; Raff, Howard V.; Mokatrin, Ahmad S.; Van Nest, Gary A.
CS Chiron Vaccines, Emeryville, CA, 94608, USA
SO Infect. Immun. (1997), 65(5), 1710-1715
CODEN: INFIBR; ISSN: 0019-9567
PB American Society for Microbiology
DT Journal
LA English
AB The ability of the adjuvant MF59 to enhance the immunogenicity of polysaccharide-protein conjugate vaccines was investigated in infant baboons. MF59 consists of stable droplets (<250 nm) of the metabolizable oil squalene and two surfactants, polyoxyethylene sorbitan monooleate and sorbitan trioleate, in an oil-in-water emulsion. In humans, MF59 is well tolerated and enhances the immunogenicity of recombinant protein subunit or particle vaccines. Its effect on the immunogenicity of polysaccharide-protein conjugate vaccines is unknown. Baboons 1-4 mo of age were immunized i.m. with N. meningitidis group C and **H. influenzae** type b (Hib) oligosaccharide-CRM197 conjugate vaccines. The lyophilized vaccines were reconstituted with phosphate-buffered saline (PBS), **Al(OH)3** (alum), or MF59. Groups of 5 animals each were given 3 injections of the resp. formulations, with one injection every 4 wk. Four weeks after each immunization, the MF59 group had up to 7-fold-higher geometric mean anticapsular-antibody titers than the alum group and 5-10-fold higher N. meningitidis group C bactericidal antibody titers. Twenty-one weeks after the 3rd immunization, the MF59 group still showed 5-10-fold-higher anticapsular antibody titers. The antibody responses of the animals given the vaccines reconstituted with PBS were low at all times measured. Both the MF59 and alum groups, but not the PBS group, showed booster antibody responses to unconjugated Hib and N. meningitidis group C polysaccharides, results consistent with induction of memory B cells. Thus, MF59 may be useful for accelerating and augmenting immunity to polysaccharide-protein conjugate vaccines in infants.

L11 ANSWER 5 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1997:145259 CAPLUS
DN 126:148484
TI Vaccine composition comprising a polysaccharide conjugate antigen adsorbed onto **aluminum phosphate**
IN Peetermans, Julien; Hauser, Pierre

PA Smithkline Beecham Biologicals S.A., Belg.; Peetermans, Julien; Hauser, Pierre
SO PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9700697	A1	19970109	WO 96-EP2690	19960619
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
CA 2222455	AA	19970109	CA 96-2222455	19960619
AU 9663591	A1	19970122	AU 96-63591	19960619
AU 696338	B2	19980910		
EP 833662	A1	19980408	EP 96-922871	19960619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
NO 9706035	A	19980216	NO 97-6035	19971222

PRAI GB 95-12827 19950623
GB 95-13443 19950701
GB 95-25657 19951215
GB 96-6032 19960322
WO 96-EP2690 19960619

AB The invention relates to a vaccine formulation for the prevention of **Hemophilus influenzae** Type B (Hib) infections and where the antigen is adsorbed onto **aluminum phosphate**. The antigen is a capsular polysaccharide from **H. influenzae** B conjugate with a carrier protein. The carrier protein is Diphtheria toxoid, Diphtheria CRM197 protein, meningococcal outer membrane protein or Tetanus toxoid. The invention also relates to a multivalent vaccine.

IT **7784-30-7, Aluminum phosphate**
RL: MOA (Modifier or additive use); USES (Uses)
(vaccine compn. comprising polysaccharide conjugate antigen adsorbed onto)

L11 ANSWER 6 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1996:548530 CAPLUS
DN 125:177440
TI Immunogenic conjugate molecules
IN Yang, Yan-Ping; Kandil, Ali; Gisonni, Lucy; Fahim, Raafat E. F.; Klein, Michel H.
PA Connaught Laboratories Limited, Can.
SO PCT Int. Appl., 64 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9621465	A2	19960718	WO 96-CA7	19960105
	WO 9621465	A3	19961010		
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN				
	US 5681570	A	19971028	US 95-371965	19950112
	CA 2210139	AA	19960718	CA 96-2210139	19960105
	AU 9643254	A1	19960731	AU 96-43254	19960105
	EP 805691	A2	19971112	EP 96-900066	19960105
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
PRAI	US 95-371965	19950112			
	WO 96-CA7	19960105			

AB Immunogenic conjugate mols. comprising at least a portion of a capsular polysaccharide of a Streptococcus strain linked to at least a portion of an outer membrane protein of a Haemophilus strain are provided in which the immunogenicity of the capsular polysaccharide is increased. Particularly capsular polysaccharide from Streptococcus pneumoniae are linked to an outer membrane protein of a **Haemophilus influenzae** strain, which protein may be the P1, P2 or particularly the P6 outer membrane protein. Conjugate mols. comprising the P6 protein linked to a capsular polysaccharide from an encapsulated pathogen other than Streptococcus are also described, in which the immunogenicity of the capsular polysaccharide is enhanced. Such conjugate mols. may be incorporated into immunogenic compns. for protecting a host against disease caused by the Streptococcus strain and preferably also the Haemophilus strain. The conjugate mols. and antibodies specific for the capsular polysaccharide or specific for the outer membrane protein may be employed in diagnostic procedures and kits. A process for individually isolating P1, P2 and P6 outer membrane proteins from a Haemophilus strain is also provided.

IT **7784-30-7, Aluminum phosphate**
21645-51-2, Aluminum hydroxide,
biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunoconjugates based on polysaccharide from Streptococcus and outer membrane protein from Haemophilus)

L11 ANSWER 7 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1996:137694 CAPLUS
DN 124:173429
TI Adjuvant compositions comprising a mineral salt and another immunostimulating compound
IN Kandil, Ali; James, Olive A.; Chong, Pele; Klein, Michel H.
PA Cannaught Laboratories Ltd., Can.
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9534308	A2	19951221	WO 95-CA359	19950615
WO 9534308	A3	19960523		
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5837250	A	19981117	US 95-483856	19950607
CA 2192659	AA	19951221	CA 95-2192659	19950615
AU 9526670	A1	19960105	AU 95-26670	19950615
EP 765163	A2	19970402	EP 95-921672	19950615
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

PRAI US 94-261194 19940616
WO 95-CA359 19950615
OS MARPAT 124:173429
AB Adjuvant compns. for modulating an immune response to an antigen administered to a host comprise a mineral salt adjuvant and at least one other adjuvant. The compns. provide an adjuvanting effect on an antigen which is greater than the adjuvanting effect attainable by one of the adjuvants alone. An antigen is covalently bonded to a glycolipid analog to provide a discrete mol. which exhibits an enhanced adjuvanting effect on the antigen which is greater than the adjuvanting effect attainable in the absence of such covalent bonding. The antigen is microbial pathogens, bacteria, viruses, proteins, glycoproteins, lipoproteins, peptides, glycopeptides, toxoids, carbohydrates, tumor-specific antigens, etc. In example, synthetic peptides were prepd. as antigen, and N-(2-L-leucine-amino-2-deoxy-.beta.-D-glucopyranosyl)-N-octadecyldodecanamide acetate, tripalmityl-Cys-Ser-Ser-Asn-Ala, tripalmityl-Cys-Ser-Glu-Glu-Glu-Glu, tripalmityl-Cys-Ser-Lys-Lys-Lys-Lys, etc. were prepd. as adjuvant. Formulations contg. these synthetic antigen and adjuvants were prepd. as vaccines for HIV, flu, RSV, PIV3, flu BHA, pertussis

toxoid, etc.

IT **7784-30-7, Aluminum phosphate**
21645-51-2, Aluminum hydroxide, uses
RL: MOA (Modifier or additive use); USES (Uses)
(adjuvant formulations contg. mineral salt and glycolipid or octadecyl ester of amino acid or lipoprotein)

L11 ANSWER 8 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1994:678850 CAPLUS
DN 121:278850
TI Vaccine compositions containing 3-O-deacylated monophosphoryl lipid A and adjuvant
IN Hauser, Pierre; Voet, Pierre; Slaoui, Moncef; Garcon-Johnson, Nathalie Marie-Josephe Claude; Desmons, Pierre
PA SmithKline Beecham Biologicals (S.A.), Belg.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9421292	A1	19940929	WO 94-EP818	19940314
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2157376	AA	19940929	CA 94-2157376	19940314
AU 9464264	A1	19941011	AU 94-64264	19940314
AU 685443	B2	19980122		
BR 9405957	A	19951212	BR 94-5957	19940314
EP 689454	A1	19960103	EP 94-911894	19940314
EP 689454	B1	19970910		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1119829	A	19960403	CN 94-191582	19940314
HU 72916	A2	19960628	HU 95-1979	19940314
JP 08508722	T2	19960917	JP 94-520640	19940314
AT 157882	E	19970915	AT 94-911894	19940314
EP 812593	A1	19971217	EP 97-101617	19940314
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, FI				
ES 2109685	T3	19980116	ES 94-911894	19940314
ZA 9401957	A	19950131	ZA 94-1957	19940321
IL 109056	A1	19980615	IL 94-109056	19940321
NO 9503759	A	19950922	NO 95-3759	19950922
FI 9504514	A	19950922	FI 95-4514	19950922

	US 5776468	A	19980707	US 96-525638	19960212
	AU 9675416	A1	19970213	AU 96-75416	19961218
PRAI	GB 93-6029	19930323			
	GB 94-3417	19940223			
	EP 94-911894	19940314			
	WO 94-EP818	19940314			

AB Novel vaccine compns. contg. small (<120-nm) particles of 3-O-deacylated monophosphoryl lipid A (I) are provided which have superior immunol. properties. When formulated with **Al(OH)3**, I interacts with **Al(OH)3** and the antigen to form a single entity. Thus, 1-20 .mu.g hepatitis B surface antigen was adsorbed onto 30-100 .mu.g **Al(OH)3** in phosphate buffer, and 30-50 .mu.g of a sonicated suspension of I was added (final vol. 600 .mu.L). Maturation of the compn. occurred during storage at 4.degree..

IT **21645-51-2, Aluminum hydroxide,** biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vaccine compns. contg. 3-O-deacylated monophosphoryl lipid A and adjuvant)

L11 ANSWER 9 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1994:62253 CAPLUS
DN 120:62253
TI Combined vaccines comprising hepatitis B surface antigen and other antigens
IN Petre, Jean; Hauser, Pierre
PA Smithkline Beecham Biologicals (S.A.), Belg.
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9324148	A1	19931209	WO 93-EP1276	19930515
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9343156	A1	19931230	AU 93-43156	19930515
	EP 642355	A1	19950315	EP 93-912750	19930515
	EP 642355	B1	19980715		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07508267	T2	19950914	JP 93-500162	19930515
	HU 71791	A2	19960228	HU 94-3366	19930515

EP 835663	A2	19980415	EP 97-204034	19930515
EP 835663	A3	19990303		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
PL 174077	B1	19980630	PL 93-306304	19930515
CZ 283910	B6	19980715	CZ 94-2892	19930515
AT 168271	E	19980815	AT 93-912750	19930515
ES 2118963	T3	19981001	ES 93-912750	19930515
ZA 9303541	A	19940621	ZA 93-3541	19930521
IL 105770	A1	19980816	IL 93-105770	19930521
CN 1085450	A	19940420	CN 93-107319	19930522
NO 9404475	A	19950118	NO 94-4475	19941122
FI 9405483	A	19950120	FI 94-5483	19941122
AU 9716480	A1	19970529	AU 97-16480	19970324

PRAI GB 92-11081 19920523
GB 92-13308 19920623
EP 93-912750 19930515
WO 93-EP1276 19930515

AB Stable and effective multivalent vaccine compns. comprising Hepatitis B surface antigen (HBsAg) are described wherein the HBsAg component is stable for 1 wk at 37.degree. and is highly immunogenic when is administered to infants. The compns. typically comprise HBsAg adsorbed to **Al phosphate** (I) and other antigens, esp. those suitable for use in a pediatrics, adsorbed to I or **Al(OH)3** (II). A conc. contg. 25,000 Lf of diphtheria toxoid and 10,000 Lf of tetanus toxoid absorbed to 0.35 g of II was prepd. in a final vol. of 0.15 L of isotonic saline and was adjusted to pH=6-7. The conc. was combined with 0.05 L of HBsAg adsorbed to I in isotonic saline and the mixt. brought to 0.5L with isotonic saline. A dose of 0.5 mL vaccine contained diphtheria toxoid 25Lf, tetanus toxoid 10Lf, and HBsAg 10.mu.g protein.

IT **21645-51-2, Aluminum hydroxide,** biological studies
RL: BIOL (Biological study)
(antigens adsorbed on, multivalent vaccine contg. hepatitis B surface antigen and)

IT **7784-30-7, Aluminum phosphate**
RL: BIOL (Biological study)
(hepatitis B surface antigen adsorbed on, multivalent vaccine contg. antigens and)

L11 ANSWER 10 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1993:678730 CAPLUS
DN 119:278730
TI Hepatitis vaccines containing 3-O-deacylated monophoshoryl lipid A
IN Garcon-Johnson, Nathalie Marie Josephe; Hauser, Pierre; Thiriart, Clothilde; Voet, Pierre
PA SmithKline Beckman Corp., Belg.
SO PCT Int. Appl., 32 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9319780	A1	19931014	WO 93-EP712	19930324
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9337516	A1	19931108	AU 93-37516	19930324
	EP 633784	A1	19950118	EP 93-906601	19930324
	EP 633784	B1	19961227		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07505372	T2	19950615	JP 93-517046	19930324
	HU 69931	A2	19950928	HU 94-2758	19930324
	AT 146678	E	19970115	AT 93-906601	19930324
	ES 2098029	T3	19970416	ES 93-906601	19930324
	CZ 283424	B6	19980415	CZ 94-2355	19930324
	IL 105161	A1	19980816	IL 93-105161	19930325
	CN 1085805	A	19940427	CN 93-105232	19930326
	FI 9404442	A	19940926	FI 94-4442	19940926
	NO 9403571	A	19941114	NO 94-3571	19940926
	AU 9664457	A1	19961107	AU 96-64457	19960905

PRAI	GB 92-6786	19920327
	GB 92-6788	19920327
	GB 92-6789	19920327
	GB 92-6797	19920327
	WO 93-EP712	19930324

AB A vaccine formulation for the treatment or prophylaxis of hepatitis, esp. hepatitis B (HB) infection, comprises a hepatitis antigen and a carrier such as alum in combination with 3-O-deacylated monophoshoryl lipid A (I). Thus, 1-20.mu.g of hepatitis B surface antigen in phosphate buffer soln. (1mg/mL) was absorbed on 30-100.mu.g of **Al(OH)3** and the soln. was then added to 30-50.mu.g of I (1mg/mL). Vol. was adjusted to 600.mu.L for providing 10 injecting doses for mice. Immunization of mice with above vaccine improved the kinetics of anti-HB response and more anti-HB antibodies was produced as compared to controls with no I.

IT **21645-51-2, Aluminum hydroxide,**
biological studies
RL: BIOL (Biological study)
(vaccine contg. hepatitis antigens and deacylated monophoshoryl lipid A and)

L11 ANSWER 11 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1993:480195 CAPLUS
DN 119:80195
TI Protein-dimeric polysaccharide conjugate vaccine
IN Marburg, Stephen; Tolman, Richard L.
PA Merck and Co., Inc., USA
SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 534764	A1	19930331	EP 92-308730	19920924
	R: CH, DE, FR, GB, IT, LI, NL				
	US 5371197	A	19941206	US 91-766242	19910924
	CA 2078359	AA	19930325	CA 92-2078359	19920916
	JP 05279399	A2	19931026	JP 92-254695	19920924

PRAI US 91-766242 19910924
AB A conjugate immunogen having polysaccharide moieties derived from bacterial sources, provides a multivalent vaccine with a low protein to polysaccharide ratio. The vaccine reduces complications assocd. with injection of protein immunogens due to pyrogenic responses, such as swelling and pain, and is particularly suitable for administration to infants. OmpC protein conjugates with polyribosyl-ribitol-phosphate (PRP) was reacted with Streptococcus pneumoniae 6A polysaccharide (PnPs6A) to obtain a gelatinous mixt., which was filtered and washed. PnPs6A-PRP-OmpC conjugate was adsorbed onto **Al(OH)**3, then was i.m. administered to chinchillas at the dose of 0.08.mu.g PnPs6A and 0.12.mu.g PRP at 0 and 4 wks and animals were bled at 0, 2, 4, 6, and 8 wks. There were high titers of both anti-PnPs6A and anti-PRP antibody.

L11 ANSWER 12 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1992:405648 CAPLUS
DN 117:5648
TI Augmentation by interleukins of the antibody response to a conjugate vaccine against **Haemophilus influenzae** b
AU Bixler, Garvin S., Jr.; Pillai, Subramonia
CS Praxis Biol., Inc., Rochester, NY, 14623, USA
SO Adv. Exp. Med. Biol. (1991), 303(Immunobiol. Proteins Pept. 6), 185-90
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal
LA English
AB Interleukins (ILs) have been recognized as potential adjuvants for use during vaccination. The immunogenicity of some poorly immunogenic bacterial capsular polysaccharides have been improved by

conjugation to a protein carrier. Augmentation of the immune response to these glycoconjugates, however, may be realized in the presence of ILs. The antibody response to one such vaccine which comprises a oligosaccharide derived from the capsule of **H. influenzae** type b coupled to CRM197 (HbOC) can be augmented in this manner. A suboptimal dose (0.1 .mu.g) of HbOC and varying concns. of IL-1.alpha. or IL-1.beta. (102-5 .times. 105 U) were injected i.m. at 0 and 2 wks into Swiss Webster mice. Vaccines were also formulated with and without **aluminum phosphate**. Antibody to the oligosaccharide was detd. by Farr assay. In 3/3 expts., IL-1.alpha. enhanced primary and secondary antibody responses whereas with IL-1.beta., only a slight increase in the primary antibody response was seen but enhanced secondary responses were obsd. Thus, IL-1.alpha. and to some extent IL-1.beta. enhanced the primary and secondary antibody responses to a glycoconjugate vaccine.

L11 ANSWER 13 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1991:427277 CAPLUS
DN 115:27277
TI A semi-synthetic vaccine involving CRM 197 as carrier for **H. influenzae** type B capsular oligosaccharides
AU Costantino, P.; Giannozzi, A.; Podda, A.; Viti, S.
CS Sclavo S.p.A., Siena, Italy
SO Zentralbl. Bakteriol., Suppl. (1990), 19(Bact. Protein Toxins), 527-8
CODEN: ZBASE2
DT Journal
LA English
AB Glycoconjugates between CRM 197 (a nontoxic deriv. of diphtheria toxin) and **Haemophilus influenzae** type B (Hib) capsular polysaccharide (3 .mu.g of oligosaccharide linked to 45 .mu.g of CRM 197 and adsorbed on 1 mg **Al(OH)3**) used as a single dose in adult volunteers elicited an increase in anti-Hib and antidiphtheria toxin antibodies and none of the humans showed adverse reactions to the product.

L11 ANSWER 14 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1988:73342 CAPLUS
DN 108:73342
TI Synergistic effect of detergents and **aluminum phosphate** on the humoral immune response to bacterial and viral membrane proteins
AU Teerlink, Tom; Beuvery, E. Coen; Evenberg, Dolf; Van Wezel, Toon L.
CS Dep. Bact. Vaccines, Natl. Inst. Public Health Environ. Hyg. (RIVM), Bilthoven, 3720 BA, Neth.
SO Vaccine (1987), 5(4), 307-14
CODEN: VACCDE; ISSN: 0264-410X
DT Journal

LA English
AB The influence of detergents on the immunogenic activity of the major outer membrane protein of Neisseria gonorrhoeae was investigated. Most detergents tested enhanced the immune response. This effect was synergistic with the adjuvant activity of **AlPO4**. The combination of detergent and **AlPO4** showed a stronger adjuvant activity than Freund's complete adjuvant. The adjuvant effect was only obsd. with protein prepns. with very low lipopolysaccharide content. The immunostimulating effect of detergents was also obsd. with meningococcal group C polysaccharide conjugated to a **Haemophilus influenzae** type b outer membrane protein and with the fusion protein of measles virus. The influence of some detergent parameters (crit. micelle concn., hydrophile-lipophile balance, and charge) was investigated.
IT **7784-30-7, Aluminum phosphate**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(immune adjuvant activity of, detergents synergism with, in response to bacterial and viral membrane proteins)

L11 ANSWER 15 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1986:223162 CAPLUS
DN 104:223162
TI Quantitative and qualitative analyses of serum antibodies elicited in adults by **Haemophilus influenzae** type b and pneumococcus type 6A capsular polysaccharide-tetanus toxoid conjugates
AU Schneerson, Rachel; Robbins, John B.; Parke, James C., Jr.; Bell, Clara; Schlesselman, James J.; Sutton, Ann; Wang, Zhen; Schiffman, Gerald; Karpas, Arthur; Shiloach, Joseph
CS Lab. Dev. Mol. Immunity, Natl. Inst. Child Health Human Dev., Bethesda, MD, 20892, USA
SO Infect. Immun. (1986), 52(2), 519-28
CODEN: INFIBR; ISSN: 0019-9567
DT Journal
LA English
AB Covalent binding to immunogenic proteins increases the immunogenicity of the capsular polysaccharides of **Haemophilus influenzae** type b (Hib) and pneumococcus type 6A (Pn6A). Conjugates composed of Hib, Pn6A, or the cross-reacting Escherichia coli K100 covalently bound to tetanus toxoid (TT) were injected into young adult volunteers. Local reactions were common and were probably due to Arthus reactivity mediated by the preexisting antibodies reacting with the TT component of the conjugates. Fever occurred in .apprx.10% of the volunteers after the 1st injection; no volunteers had fever after the 2nd injection. Similar levels of Hib or Pn6A antibodies were elicited by either 50- or 100-.mu.g doses or by concurrent injection of 2 different conjugates (Hib-TT and Pn6A-TT or Hib-TT and

K100-TT). The Hib-TT elicited about a 180-fold increase in Hib antibodies, and the Pn6A-TT conjugate elicited about an 8-fold increase in Pn6A antibodies after 1 injection. Booster reactions were not elicited in adults; similar levels of antibodies in the 5 exptl. groups suggested that the responses elicited by the conjugates were maximal. A 1-way cross-reaction was noted as Pn6A conjugates elicited rises of Hib antibodies in 13 of 20 volunteers; only 4 of 59 volunteers immunized with Hib-TT had increases in Pn6A antibodies. The preimmunization Hib antibodies were composed of IgM, IgA, and IgG. The postimmunization sera showed an increase in all 3 isotypes; the elevation of the IgG was the highest of the 3 isotypes. Conjugate-induced antibodies to both the polysaccharide and TT-exerted biol. activities that have been correlated with immunity. Adsorption of the Hib-TT onto **Al hydroxide** resulted in higher levels and an earlier Hib antibody response in infant rhesus. These results encourage the evaluation of Hib and Pn6A conjugates in human children and infants.

L11 ANSWER 16 OF 16 CAPLUS COPYRIGHT 1999 ACS
AN 1985:539889 CAPLUS
DN 103:139889
TI Enhancement of immunogenic activity of ribosomal preparations from **Haemophilus influenzae** by various adjuvants
AU Cabrera-Contreras, R.; Plescia, O.; Solotorovsky, M.; Lynn, M.
CS Waksman Inst. Microbiol., Rutgers Univ., New Brunswick, NJ, 08903, USA
SO Vaccine (1985), 3(2), 103-8
CODEN: VACCDE
DT Journal
LA English
AB Ribosomes from **H. influenzae** type b have been reported to have immunoprotective activity in animals whos immunity can be enhanced by adjuvants. In this report the adjuvant activity was evaluated from several compds. in conjunction with ribosomes from the b and c serotypes of **H. influenzae**. Alhydrogel, saponin and diphtheria-pertussis-tetanus vaccine were found to significantly enhance the immunoprotective response in mice, equally or exceeding the activity of Freund's incomplete adjuvant. All of these adjuvants also enhanced significantly the IgM response of mice to sheep red blood cells. Ribosomes also enhanced this response. Among the compds. failing to provide adjuvant activity for ribosomes were poly(A:U), muramyl dipeptide, mycobacterial ext., dimethylglycine, methylated bovine serum albumin, sodium diethylthiocarbamate, and cetyltrimethylammonium bromide.
IT **21645-51-2**, biological studies
RL: BIOL (Biological study)
(immunogenicity of **Haemophilus influenzae** ribosome enhancement by)

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB, DRUGLAUNCH' ENTERED AT 12:50:06 ON 25 MAR 1999)

L12 107 SEA ABB=ON PLU=ON L10
L13 105 SEA ABB=ON PLU=ON L12 NOT L7
L14 80 DUP REM L13 (25 DUPLICATES REMOVED)
L15 55 SEA ABB=ON PLU=ON L14 AND (ADJUVANT OR IMMUNIS? OR IMMUNIZ? OR VACCIN? OR IMMUNOGEN?)
L16 16 SEA ABB=ON PLU=ON L15 AND ADMIN?

L16 ANSWER 1 OF 16 MEDLINE
AN 97270468 MEDLINE
DN 97270468
TI MF59 **adjuvant** enhances antibody responses of infant baboons **immunized** with **Haemophilus influenzae** type b and Neisseria meningitidis group C oligosaccharide-CRM197 conjugate **vaccine**.
AU Granoff D M; McHugh Y E; Raff H V; Mokatrin A S; Van Nest G A
CS Chiron Vaccines, Emeryville, California 94608, USA..
danvgranoff@cc.chiron.com
SO INFECTION AND IMMUNITY, (1997 May) 65 (5) 1710-5.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199707
AB The ability of the **adjuvant** MF59 to enhance the **immunogenicity** of polysaccharide-protein conjugate **vaccines** was investigated in infant baboons. MF59 consists of stable droplets (<250 nm) of the metabolizable oil squalene and two surfactants, polyoxyethylene sorbitan monooleate and sorbitan trioleate, in an oil-in-water emulsion. In humans, MF59 is well tolerated and enhances the **immunogenicity** of recombinant protein subunit or particle **vaccines**. Its effect on the **immunogenicity** of polysaccharide-protein conjugate **vaccines** is unknown. Baboons 1 to 4 months of age were **immunized** intramuscularly with Neisseria meningitidis group C and **Haemophilus influenzae** type b (Hib) oligosaccharide-CRM197 conjugate **vaccines**. The lyophilized **vaccines** were reconstituted with phosphate-buffered saline (PBS), **Al(OH)**3 (alum), or MF59. Groups of five animals each were given three injections of the respective formulations, with one injection every 4 weeks. Four weeks after each **immunization**, the MF59 group had up to 7-fold-higher geometric mean anticapsular-antibody titers than the alum group and 5- to 10-fold-higher N. meningitidis group C bactericidal-antibody titers. Twenty-one weeks after the third **immunization**, the

MF59 group still showed 5- to 10-fold-higher anticapsular-antibody titers. The antibody responses of the animals given the **vaccines** reconstituted with PBS were low at all times measured. Both the MF59 and alum groups, but not the PBS group, showed booster antibody responses to unconjugated Hib and N. meningitidis group C polysaccharides, results consistent with induction of memory B cells. Thus, MF59 may be useful for accelerating and augmenting immunity to polysaccharide-protein conjugate **vaccines** in infants.

L16 ANSWER 2 OF 16 MEDLINE
AN 92214276 MEDLINE
DN 92214276
TI Augmentation by interleukins of the antibody response to a conjugate **vaccine** against **Haemophilus influenzae** b.
AU Bixler G S Jr; Pillai S
CS Praxis Biologics, Inc., Rochester, New York 14623..
SO ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1991) 303 185-90. Journal code: 2LU. ISSN: 0065-2598.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199207
AB Interleukins have been recognized as potential **adjuvants** for use during **vaccination**. The **immunogenicity** of some poorly **immunogenic** bacterial capsular polysaccharides have been improved by conjugation to a protein carrier. Augmentation of the immune response to these glycoconjugates, however, may be realized in the presence of interleukins. The antibody response to one such **vaccine** which comprises a oligosaccharide derived from the capsule of **Haemophilus influenzae** type b coupled to CRM197 (HbOC) can be augmented in this manner. A suboptimal dose (0.1 microgram) of HbOC and varying concentrations of IL-1 alpha or IL-1 beta (10(2) - 5 x 10(5) U) were injected intramuscularly at 0 and 2 weeks into Swiss Webster mice. **Vaccines** were also formulated with and without **aluminum phosphate**. Antibody to the oligosaccharide was determined by Farr assay. In 3/3 experiments, IL-1 alpha enhanced primary and secondary antibody responses whereas with IL-1 beta, only a slight increase in the primary antibody response was seen but enhanced secondary responses were observed. Thus, IL-1 alpha and to some extent IL-1 beta enhanced the primary and secondary antibody responses to a glycoconjugate **vaccine**.

L16 ANSWER 3 OF 16 MEDLINE
AN 90271024 MEDLINE

DN 90271024
TI Duration of serum antibodies elicited by **Haemophilus influenzae** type b capsular polysaccharide alone or conjugated to tetanus toxoid in 18- to 23-month-old children.
AU Claesson B A; Schneerson R; Trollfors B; Lagergard T; Taranger J; Robbins J B
CS Department of Infectious Diseases, University of Goteborg, Sweden..
SO JOURNAL OF PEDIATRICS, (1990 Jun) 116 (6) 929-31.
Journal code: JLZ. ISSN: 0022-3476.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199009

L16 ANSWER 4 OF 16 MEDLINE
AN 86283798 MEDLINE
DN 86283798
TI **Immunogenicity** in infants of **Haemophilus influenzae** type B polysaccharide in a conjugate **vaccine** with Neisseria meningitidis outer-membrane protein.
AU Einhorn M S; Weinberg G A; Anderson E L; Granoff P D; Granoff D M
NC RO1 AI 17962 (NIAID)
T32 AI 07172 (NIAID)
RR-36 (NCRR)
SO LANCET, (1986 Aug 9) 2 (8502) 299-302.
Journal code: L0S. ISSN: 0140-6736.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 198611
AB 63 children, aged 2-17 months, were given a new conjugate **vaccine** composed of the capsular polysaccharide of **Haemophilus influenzae** type b linked to a Neisseria meningitidis outer-membrane protein. Subjects under 7 months received two injections separated by 1 month, and older subjects received either one or two injections. There were no systemic reactions to this **vaccine** when it was given with **aluminium hydroxide**. A single injection of **vaccine** was highly **immunogenic**; the geometric mean serum anticapsular antibody concentrations before **immunisation** and 1 month later were 0.35 microgram/ml and 0.98 microgram/ml for babies of 2-3 months, 0.12 microgram/ml and 1.85 micrograms/ml for those of 4-6 months, and 0.15 microgram/ml and 4.1 micrograms/ml for those of 8-17 months (p less than or equal to 0.003 for each age group). After a second injection of **vaccine**, 80% and 76% of infants of 2-3 and 4-6 months, respectively, had antibody concentrations greater than 1.0

micrograms/ml. Most subjects showed evidence of IgG responses as measured by enzyme-linked immunosorbent assay. 6-12 months after **immunisation**, serum antibody levels had fallen (p less than 0.05) but they remained higher than those of unimmunized controls (p less than 0.001).

L16 ANSWER 5 OF 16 MEDLINE
AN 86194736 MEDLINE
DN 86194736
TI Quantitative and qualitative analyses of serum antibodies elicited in adults by **Haemophilus influenzae** type b and pneumococcus type 6A capsular polysaccharide-tetanus toxoid conjugates.
AU Schneerson R; Robbins J B; Parke J C Jr; Bell C; Schlesselman J J; Sutton A; Wang Z; Schiffman G; Karpas A; Shiloach J
SO INFECTION AND IMMUNITY, (1986 May) 52 (2) 519-28.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198608
AB Covalent binding to **immunogenic** proteins increases the **immunogenicity** of the capsular polysaccharides of **Haemophilus influenzae** type b (Hib) and pneumococcus type 6A (Pn6A). Conjugates composed of Hib, Pn6A, or the cross-reacting Escherichia coli K100 covalently bound to tetanus toxoid (TT) were injected into young adult volunteers. Local reactions were common and were probably due to Arthus reactivity mediated by the preexisting antibodies reacting with the TT component of the conjugates. Fever occurred in about 10% of the volunteers after the first injection; no volunteers had fever after the second injection. Similar levels of Hib or Pn6A antibodies were elicited by either 50- or 100-micrograms doses or by concurrent injection of two different conjugates (Hib-TT and Pn6A-TT or Hib-TT and K100-TT). The Hib-TT elicited about a 180-fold increase in Hib antibodies, and the Pn6A-TT conjugate elicited about an 8-fold increase in Pn6A antibodies after one injection. Booster reactions were not elicited in adults; similar levels of antibodies in the five experimental groups suggested that the responses elicited by the conjugates were maximal. A one-way cross-reaction was noted as Pn6A conjugates elicited rises of Hib antibodies in 13 of 20 volunteers; only 4 of 59 volunteers **immunized** with Hib-TT had increases in Pn6A antibodies. The preimmunization Hib antibodies were composed of immunoglobulin M (IgM), IgA, and IgG. The postimmunization sera showed an increase in all three isotypes; the elevation of the IgG was the highest of the three isotypes. Conjugate-induced antibodies to both the polysaccharide and TT exerted biological activities that have been correlated with

immunity. Adsorption of the Hib-TT onto **aluminium hydroxide** resulted in higher levels and an earlier Hib antibody response in infant rhesus. These results encourage the evaluation of Hib and Pn6A conjugates in human children and infants.

L16 ANSWER 6 OF 16 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 97345547 EMBASE
DN 1997345547
TI Fatal hyperphosphatemia after oral phosphate overdose in a premature infant.
AU Perlman J.M.
CS Prof. J.M. Perlman, Department of Pediatrics, Texas Univ. Southwestern Med. Ctr., 5323 Harry Hines Boulevard, Dallas, TX 75235-9063, United States. jperlm@mednet.swmed.edu
SO American Journal of Health-System Pharmacy, (1997) 54/21 (2488-2490).
Refs: 11
ISSN: 1079-2082 CODEN: AHSPEK
CY United States
DT Journal; Article
FS 007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
052 Toxicology
LA English

L16 ANSWER 7 OF 16 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 93042540 EMBASE
DN 1993042540
TI **Vaccine** development: Progression from target antigen to product.
AU Ellis R.W.
CS Cellular and Molecular Biology, Merck Sharp and Dohme Research Lab.,West Point, PA 19486, United States
SO Advances in Experimental Medicine and Biology, (1992) 327/- (263-271).
CODEN: AEMBAP
CY United States
DT Journal; Conference Article
FS 004 Microbiology
007 Pediatrics and Pediatric Surgery
017 Public Health, Social Medicine and Epidemiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English

L16 ANSWER 8 OF 16 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-145667 [18] WPIDS
DNC C94-066614
TI Combined paediatric **vaccine** compsn. - comprising a mixt.

of diphtheria, tetanus, pertussis and **Haemophilus influenzae** type b antigens.

DC B04 D16

IN HACKELL, J G; HOGERMAN, D A; MADORE, D V; PARADISO, P R

PA (AMCY) AMERICAN CYANAMID CO

CYC 27

PI EP 594950 A1 940504 (9418)* EN 10 pp
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
NO 9303856 A 940428 (9424)
AU 9350290 A 940512 (9425)
FI 9304725 A 940428 (9426)
CA 2109159 A 940428 (9428)
CZ 9302272 A3 940518 (9428)
NZ 250029 A 940927 (9438)
HU 67239 T 950328 (9518)
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AU 669570 B 960613 (9631)
IL 107387 A 970415 (9726)
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EP 594950 B1 990127 (9909) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

ADT EP 594950 A1 EP 93-111735 930722; NO 9303856 A NO 93-3856 931026; AU 9350290 A AU 93-50290 931026; FI 9304725 A FI 93-4725 931026; CA 2109159 A CA 93-2109159 931025; CZ 9302272 A3 CZ 93-2272 931026; NZ 250029 A NZ 93-250029 931022; HU 67239 T HU 93-3028 931026; TW 256774 A TW 93-106371 930810; JP 07300427 A JP 93-285570 931021; AU 669570 B AU 93-50290 931026; IL 107387 A IL 93-107387 931025; CZ 283587 B6 CZ 93-2272 931026; SG 47725 A1 SG 96-4072 930722; EP 594950 B1 EP 93-111735 930722

FDT AU 669570 B Previous Publ. AU 9350290; CZ 283587 B6 Previous Publ. CZ 9302272

PRAI US 92-966995 921027

AN 94-145667 [18] WPIDS

AB EP 594950 A UPAB: 960129
Combined paediatric **vaccine** compsn. comprising, in a single **immunising** dose, a mixt. of (i) diphtheria, tetanus and pertussis antigens and (ii) a conjugate of fragments of the capsular polysaccharide antigen of **Haemophilus influenzae** type b and CRM197 protein, in an aq. vehicle. The combine **vaccine** compsn. provides enhanced antibody response, by infants, to each of the diphtheria, tetanus, pertussis and **Haemophilus influenzae** type b **vaccine** components.

The diphtheria, antigen is diphtheria toxoid (esp. adsorbed on **aluminium phosphate**), the tetanus antigen is tetanus toxoid (esp. adsorbed on **aluminium phosphate**), and the pertussis antigen is inactive Bordetella

pertussis cells (esp. suspended in a soln. contg. potassium phosphate monobasic, sodium phosphate dibasic and sodium chloride). **Admin.** is esp. intramuscular.

ADVANTAGE - The combination **vaccine** exhibits improved **immunogenicity** in infants for each of the four **vaccine** components when compared to DTP and **Haemophilus influenzae** type b conjugate **vaccines administered** concurrently but separately. The **vaccines** are safe to use.

Dwg.0/0

Dwg.0/0

L16 ANSWER 9 OF 16 SCISEARCH COPYRIGHT 1999 ISI (R)

AN 1998:235986 SCISEARCH

GA The Genuine Article (R) Number: BK54S

TI Biodegradable polymer microspheres as **vaccine adjuvants** and delivery systems

AU Gupta R K (Reprint); Chang A C; Siber G R

CS WYETH LEDERLE VACCINES & PEDIAT, 401 N MIDDLETOWN RD, PEARL RIVER, NY 10965 (Reprint)

CYA USA

SO DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (MAR 1998) Vol. 92, pp. 63-78.
Publisher: KARGER, POSTFACH, CH-4009 BASEL, SWITZERLAND.
ISSN: 0301-5149.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 83

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Though **vaccination** has been the most cost-effective way of controlling infectious diseases, the logistics of delivering at least two to three doses of conventional **vaccines** for primary **immunization** to achieve protection are difficult and compliance is frequently inadequate, particularly in developing countries. In recent years biodegradable polymer microspheres have received much attention for the purposes of controlled release of antigens, (i) to reduce the number of doses needed for primary **immunization** to as few as a single dose and (ii) to target an antigen to microfold cells on mucosal surfaces after oral **administration** or to antigen-presenting cells after parenteral inoculations. A variety of **vaccine** antigens have been encapsulated in microspheres usually composed of poly (lactic/glycolic) acid (PLGA). Based on the size of the microspheres, molecular weight of polymer and ratio of lactic to glycolic acid in the polymer, the antigen may be targeted to various cells of the immune system or it may form a depot at the site of injection, allowing the slow release of the antigen for extended periods. Additionally, another **adjuvant** may be

incorporated inside microspheres together with the antigen, further enhancing or modulating the immune response to the desired type. The major problems in developing controlled-release **vaccines** include instability of **vaccine** antigens during micro-encapsulation, storage and subsequent hydration. We encapsulated tetanus toroid (TT) and **Haemophilus influenzae** type b capsular polysaccharide conjugated to TT (Hib-T) inside PLGA microspheres and evaluated the antibody levels in mice. A single injection of these micro-encapsulated **vaccines** elicited high antibody levels which persisted for several months. The antibody levels were similar or superior to those elicited by conventional formulations of **AlPO4** -adsorbed TT or soluble Hib-T conjugate **vaccine**.

L16 ANSWER 10 OF 16 PROMT COPYRIGHT 1999 IAC

AN 1998:284484 PROMT
TI Conference Coverage (ECPI Combination **Vaccines**) Many Hurdles for Successful Combination **Vaccines**
SO Vaccine Weekly, (8 Jun 1998) pp. N/A.
ISSN: 1074-2921.
LA English
WC 1182
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB It's more than just mixing.
Combinations of existing **vaccines** are more than the sum of their parts: they are complex new **vaccine** entities.
Developers wishing to take advantage of the trend toward combination **vaccines** must make similarly complex plans, and must do so early in the course of combination **vaccine** development.
"There are significant challenges to the development and implementation of combination **vaccines**," warned Ronald Ellis, senior director of **vaccine** research and development for Astra Research Center, Boston, Massachusetts. "An integrated development plan should be established early in the program."
Ellis discussed strategies for making such plans in an address to the European Center for Pharmaceutical Information (ECPI) Rapid Development of Combination **Vaccines** Conference, held April 20-22, 1998, in London, England.
After facing the technical challenges of creating a combination **vaccine** and the clinical challenges of proving its efficacy, it would seem that the job would be done. But equally formidable regulatory, manufacturing, and marketing challenges still remain.
"All these issues must be planned to have a successful **vaccine** in the end," Ellis said.
One the most important technical challenges to combination **vaccines** stems from the fact that many component **vaccines** are formulated with aluminum salts as **adjuvants**. But different **vaccines** may use

aluminum hydroxide, aluminum hydroxyphosphate, or **aluminum phosphate**.
"Aluminum-adsorbed antigens may encounter and exchange onto the 'new' aluminum," Ellis observed. "And non-adsorbed antigens may bind to aluminum."
Such interactions, difficult to foresee, may significantly affect the **immunogenicity** of component **vaccines**.
Other physical interactions that may cause problems are those with excipients, or additives, used to stabilize component **vaccines**. These chemicals may have unexpected effects on other **vaccine** antigens.
Moreover, the different **vaccines** may themselves interact in ways that discourage proper use: by causing clumping, aggregation, discoloration, or by needing vigorous mixing.
Sometimes an ingenious solution is required. Ellis pointed to the example of the combined diphtheria-tetanus-whole-cell pertussis (DTPw) and intravenous polio **vaccine** (IPV). DTPw is preserved with thimerosal, which over time destroys IPV and thus makes it impossible to store the combined **vaccines**.

L16 ANSWER 11 OF 16 PROMT COPYRIGHT 1999 IAC

AN 1998:274239 PROMT
TI Primer on **vaccinations**
Lengthy article of an introductory nature
AU Sindelar, Robert D.
SO Drug Topics, (18 May 1998) pp. 81.
ISSN: 0012-6616.
LA English
WC 5375
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB INTRODUCTION
Vaccinations are among the most cost-effective and widely used public health interventions. Yet public concerns focus on the health risks associated with **vaccines** as much as on the reduction in incidence of **vaccine**-preventable diseases.
Pharmacists can play an important role as **vaccination** leaders in **immunization** advocacy, in patient and health-care education, and in the role of **immunizers**. As pharmacists develop these expanding roles, a review of the principles of **vaccination** may prove useful. While this article can provide only the basics, the reader is encouraged to use it as a foundation for further studies.
The immune response. The human immune system is a complex regulatory and surveillance system composed of interacting immune cells, various tissues, mediators, and immunoglobulins (antibody molecules). Host-protective in nature, the immune system inactivates invading microorganisms, detects and rejects tumors, neutralizes

toxins, and performs other host-defense functions.
Immunogens are substances that can evoke an immune response with the production of immunoglobulins; an **immunogen** that can itself combine with an immune response-generated immunoglobulin is an antigen. In simplest terms, the immune system cells fall into two general categories that interact with each other: lymphocytes (T-lymphocytes or T-cells and B-lymphocytes or B-cells) that recognize antigens (in effect, **immunization**) on the surface of invading pathogens and cancer cells; and phagocytes, cells that internalize pathogens and degrade them.
There is a very important difference between the two categories: The response of specific (adaptive) immunity, involving the B- and T-lymphocytes, improves with each successive exposure to the same antigen. This "immunological memory" results from the clonal selection of genetically specific B- and T-lymphocytes (memory cells). The response of nonspecific (innate) immunity, involving phagocytic cells, physical/chemical barriers, and the complement cascade does not change upon repeated exposure to a given antigen. Specific immunity may be further divided into humoral immunity (immunity attributable to B-lymphocytes and immunoglobulins) and cellular immunity (mediated by specifically sensitized T-lymphocytes).

L16 ANSWER 12 OF 16 PROMT COPYRIGHT 1999 IAC

AN 96:518038 PROMT
TI Merck & Co. Inc.: Comvax (Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) **Vaccine**)
SO PR Newswire, (4 Oct 1996) pp. 1004NYF012.
LA English
WC 5155
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB WEST POINT, Pa., Oct. 4 /PRNewswire/ -- The following was released today by Merck & Co. Inc.:
DESCRIPTION
COMVAX(TM)* (Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) **Vaccine**) is a sterile bivalent **vaccine** made of the antigenic components used in producing PedvaxHIB(R) (Haemophilus b Conjugate **Vaccine** (Meningococcal Protein Conjugate)) and RECOMBIVAX HB(R) (Hepatitis B **Vaccine** (Recombinant)). These components are the **Haemophilus influenzae** type b capsular polysaccharide (PRP) that is covalently bound to an outer membrane protein complex (OMPC) of Neisseria meningitidis and hepatitis B surface antigen (HBsAg) from recombinant yeast cultures. **Haemophilus influenzae** type b and Neisseria meningitides serogroup B are grown in complex fermentation media.

The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from Neisseria meningitidis is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration.
The PRP-OMPC conjugate is prepared by the chemical coupling of the highly purified PRP (polyribosylribitol phosphate) of **Haemophilus influenzae** type b (Haemophilus b, Ross strain) to an OMPC of the B11 strain of Neisseria meningitidis serogroup B. The coupling of the PRP to the OMPC, which is necessary for enhanced **immunogenicity** of the PRP, is confirmed by analysis of the conjugate's components following chemical treatment which yields a unique amino acid. After conjugation, the aqueous bulk is then adsorbed onto an **aluminum hydroxide adjuvant.**
HBsAg is produced in recombinant yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast, and the **vaccine** for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories. The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast Saccharomyces cerevisiae containing the gene for the adw subtype of HBsAg. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The **vaccine** contains no detectable yeast DNA but may contain not more than 1% yeast protein. The aqueous bulk is treated with formaldehyde and then adsorbed onto an **aluminum hydroxide adjuvant.**

L16 ANSWER 13 OF 16 PROMT COPYRIGHT 1999 IAC

AN 92:121754 PROMT
TI Havrix launch gives SB head start
SO Pharmaceutical Business News, (7 Feb 1992) pp. N/A.
LA English
WC 792
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB VIENNA -- The launch of Havrix, the first **vaccine** against Hepatitis A, has given manufacturers SmithKline Beecham Biologicals a head start into the hepatitis A market - currently estimated to be worth GBP150-GBP200 million.
The **vaccine**, recently launched in Switzerland and Belgium is expected to get its UK licence within a matter of weeks. Submissions have also been made in Germany, and the US application will take place mid-1992.
At a conference in Vienna, Jean Stephenne, general manager and vice-president of Rixensart (Belgium) based SmithKline Beecham Biologicals said that he expected up to three competitors to launch

vaccines against hepatitis A.
"We have a 12 to 18 month lead over our nearest competitor (Merck) in the European market," said Stephenne.
The Vienna conference heard infectious disease specialists outline the main target groups for the **vaccine**. These will be international travellers from developed countries to regions of high hepatitis A endemicity, and people working in certain "at risk occupations". The latter include staff and residents of day care centres, sewerage workers, food handlers, nursing and other health care staff, people living in military barracks or other crowded institutions, homosexuals and IV drug abusers.
Havrix is a sterile suspension of formaldehyde-inactivated hepatitis A virus (HM175 hep A strain) absorbed onto **aluminium hydroxide**. Internationally the cost of the **vaccine** will be pitched at a similar level to SB's recently launched hepatitis B **vaccine** Engerix-B, around GBP10 a dose.
A primary course of two 1 ml doses are **administered** one month apart. A booster one year after the initial course is expected to extend protection for up to 10 years, according to SB.

L16 ANSWER 14 OF 16 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-27097 DRUGU T M S G
TI **Immunogenicity** of a five-component acellular pertussis **vaccine** in infants and young children.
AU Halperin S A; Barreto L; Friesen B; Meekison W
CS Univ.Dalhousie; Connaught-Lab.
LO Halifax, Nova Scotia, Willowdale, Ontario, Calgary, Alberta, Surrey, British Columbia, Canada
SO Arch.Pediatr.Adolesc.Med. (148, No. 5, 495-502, 1994) 3 Tab. 41 Ref.
AV Izaak Walton Killam Children's Hospital, 5850 University Ave, Halifax, Nova Scotia, Canada B3J 3G9.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 94-27097 DRUGU T M S G
AB A study of 159 children indicated that 4- and 5-component acellular pertussis **vaccines** (CP4 and CP5; Connaught) were safe and **immunogenic** and that the 5th component, a 69-kDa membrane protein, did not increase side-effects. 137 Children were randomized to receive i.m. CP4 or CP5 alone or combined with diphtheria and tetanus toxoids (CP4DT or CP5DT, respectively) in a double-blind manner. 22 Children received i.m. CP5DT (non-blind). **Haemophilus influenzae vaccine** was also **administered** to children receiving CP4, CP5 and CP5DT **vaccines**. All components of CP4 and CP5 induced Ab

responses. Side-effects were not significantly different between **vaccines** and included local reactions (tenderness, erythema, swelling and hardness) and mild/moderate systemic reactions (irritability, fever, crying, drowsiness, listlessness, pallor, reduced appetite, vomiting and diarrhea).

ABEX Methods 137 Children (aged 17-18 mth), scheduled to receive their 4th diphtheria + pertussis + tetanus **vaccine**, received 0.5 ml CP4 (n = 35), CP5 (n = 33), CP4DT (n = 35) or CP5DT (n = 34) followed 1 mth later by **Haemophilus influenzae vaccine** and, in the case of CP4 and CP5 recipients, DT toxoids were **administered**. 22 Children (aged 4-6 yr) received CP5DT. Results CP4 and CP5 (0.5 ml) contained pertussis toxin (PT; 10 ug), filamentous hemagglutinin (5 ug) and fimbriae 2 and 3 (5 ug); CP5 also contained 69-kDa protein (3 ug). CP4, CP5, CP4DT and CP5DT were adsorbed to **aluminum phosphate** (1.5 mg) and contained 0.6% 2-phenoxyethanol as preservative. Local reactions (mainly tenderness) occurred in 8.6-29.4% of 17-18 mth-old children and 71.4% of 4-6 yr-old children; 1 child in the latter group had a swelling of 70 mm but no younger child had a swelling over 35 mm. Systemic reactions (mainly irritability) occurred in 40-65.7% of 17-18 mth-old children and 38.1% of 4-6 yr-old children; fever/feverishness occurred in 20% but no temperature was above 39 deg. Local and systemic reactions were more frequent with CP5 and CP5DT but this did not achieve significance. Ab responses were mainly IgG. Ab response to PT was less than expected in all groups; 55-66% had at least 4-fold increase in PT-neutralizing titer (Chinese hamster ovary cell cytotoxicity) and 88-100% had a similar increase by ELISA. Previous doses had been Canadian whole-cell **vaccine**, thus, this represented the 1st exposure to PT. Ab response to the 69-kDa protein was marked in CP5 recipients but slight increase was observed in CP4 recipients. (W2/KP)

L16 ANSWER 15 OF 16 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 90-19710 DRUGU M
TI Opsonophagocidal Activity in Sera from Infants and Children **Immunized** with **Haemophilus influenzae** Type b Conjugate **Vaccine** (Meningococcal Protein Conjugate).
AU Gray B M
LO Birmingham, Alabama, United States
SO Pediatrics (85, No. 4, Pt. 2, 694-97, 1990) 1 Fig. 1 Tab. 17 Ref.
CODEN: PEDIAU ISSN: 0031-4005
AV Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL 35294, U.S.A.
LA English
DT Journal
FA AB; LA; CT

Searcher : Shears 308-4994

FS Literature
AN 90-19710 DRUGU M
AB I.m. **administration** of 1 or 2 doses of **Haemophilus influenzae** type b capsular polysaccharide (polyribosylribitol phosphate, PRP) conjugated to an outer membrane protein complex (OMPC) from Neisseria meningitidis group B (PedvaxHIB) to 97 children aged 2-18+ mth resulted in excellent antibody responses and promotion of opsonophagocidal activity in sera, even in the youngest age group. 3 Different **vaccine** lots, 1072, 1080 and 1085 induced similar antibody and immune responses. Overall, 94% of **vaccinees** responded as measured using RIA of the anti-PRP antibody levels in sera, and functional measurements of opsonophagocidal activity.
ABEX Methods 3 Different lots of **vaccine**, 1072, 1080 and 1085 were **administered** i.m. at 15 ug after being adsorbed to **aluminum hydroxide**.Children 12 mth and older received a single dose, while those younger than 18 mth received 2 doses with a 2 mth interval. Results Nearly all sera obtained from the 97 participants prior to **vaccination** had RIA antibody levels of less than 1 ug/ml, and opsonophagocidal activity of less than 50% killing of the inoculum. Sera obtained after the 1st dose of **vaccine** generally had over 1 ug/ml of antibody, and opsonophagocidal activity over 50% in 90% of **vaccinees**. There appeared to be an all-or-nothing effect in the opsonophagocytic test. There were no significant differences in the response elicited by the 3 different **vaccine** lots. Responses were greater among children older than 18 mth, and least in those younger than 6 mth. Nevertheless, 80% of the youngest infants had anti-PRP antibody levels in excess of 1 ug/ml and had opsonophagocidal activity. 3 Infants less than 12 mth old had anti-PRP levels just below the cut-off value. All 3 responded well to the 2nd dose leaving only 2 infants in that age group who failed to respond with levels of 1 ug/ml after receiving the 2nd dose of **vaccine**. 2 Children in each of the older age groups failed to respond after a single dose of **vaccine** . Thus 94% of **vaccinees** responded with antibody as measured by the RIA and functional methods. (B27/LPD)

L16 ANSWER 16 OF 16 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 88-21442 DRUGU T M S
TI Bacterial **Vaccines** for Splenectomized Patients.
AU Kafidi K T; Rotschafer J C
LO St. Paul, Minnesota, United States
SO Drug Intell.Clin.Pharm. (22, No. 3, 192-97, 1988) 1 Tab. 65 Ref.
CODEN: DICPBB
AV College of Pharmacy, University of Minnesota and Department of Clinical Pharmacy, St. Paul-Ramsey Medical Center, 640 Jackson St., St. Paul, MN 55101, U.S.A.
LA English

Searcher : Shears 308-4994

DT Journal
FA AB; LA; CT
FS Literature
AN 88-21442 DRUGU T M S
AB Asplenic persons are at increased risk of serious bacterial infection, particularly due to Strept. pneumoniae, **Hemophilus influenzae** and Neisseria meningitidis. **Vaccines** that are available for these common pathogens are reviewed. None is 100% effective, and the concept of ongoing antibiotic cover is discussed. The safety profiles of the currently available **vaccines** weigh heavily in favor of routine **vaccination**. Recommendations for the use of these **vaccines** are given.

ABEX Strept. pneumoniae is responsible for about 50% of post-splenectomy infections, but **Hemophilus influenzae** and Neisseria meningitidis are also important pathogens. Mortality can be as high as 50-80% despite prompt antibiotic therapy. Strept. pneumoniae **vaccine** recommendations are outlined, and include patients aged over 65, asplenic patients, and patients with immunodeficiency syndromes. The new 23-valent **vaccine** is about 85% effective in asplenic patients over 15 yr old. Protection lasts about 2 yr, and **vaccination** may be more effective if **administered** prior to splenectomy. Adverse reactions include fever, erythema, pain and swelling, and severe localized and systemic reactions may occur with booster doses. Penicillin V prophylaxis is recommended along with the **vaccination**, and erythromycin may be employed in patients with penicillin intolerance. 2 Different types of hemophilus type B **vaccine** exist currently with 1 being conjugated to diptheria toxoid, and recommendations as to their use are based on studies in children. The conjugate **vaccine** is more **immunogenic** than the polysaccharide **vaccine**, and can be used in younger children, and tolerance is good. Rifampicin prophylaxis is mentioned. Neisseria meningitidis **vaccine** is available in a tetravalent lyophilized form, and **adjuvants** include **aluminum phosphate**. Adverse effects include localized erythema and transient fever. (B27/LPD) (J.C.R.)

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB, DRUGLAUNCH' ENTERED AT 12:57:07 ON 25 MAR 1999)

Author (s)

L17 306 S LOOSMORE S?/AU
L18 21447 S YANG Y?/AU
L19 1208 S CHONG P?/AU
L20 12005 S KLEIN M?/AU
L21 42 S L17 AND L18 AND L19 AND L20
L22 236 S L17 AND (L18 OR L19 OR L20)
L23 147 S L18 AND (L19 OR L20)

Searcher : Shears 308-4994

L24 284 S L19 AND L20
L25 34299 S L17 OR L18 OR L19 OR L20
L26 252 S (L21 OR L22 OR L23 OR L24 OR L25) AND L1
L27 97 DUP REM L26 (155 DUPLICATES REMOVED)
L28 11 S L27 AND ADMIN?

=> d 1-11 bib abs

L28 ANSWER 1 OF 11 CAPLUS COPYRIGHT 1999 ACS
AN 1998:414012 CAPLUS
DN 129:174401
TI A 20-kilodalton N-terminal fragment of the D15 protein contains a protective epitope(s) against **Haemophilus influenzae** type a and type b
AU **Yang, Yan-Ping**; Thomas, Wayne R.; **Chong, Pele**; **Loosmore, Sheena M.**; **Klein, Michel H.**
CS Research Center, Pasteur Merieux Connaught Canada, North York, ON, M2R 3T4, Can.
SO Infect. Immun. (1998), 66(7), 3349-3354
CODEN: INFIBR; ISSN: 0019-9567
PB American Society for Microbiology
DT Journal
LA English
AB A conserved 80-kDa minor outer membrane protein, D15, of **H. influenzae** has been shown to be a protective antigen in lab. animals against **H. influenzae** type a (Hia) or type b (Hib) infection. To localize the protective B-cell epitope(s) within the D15 protein and to further explore the possibility of using synthetic peptides as vaccine antigens, a 20-kDa N-terminal fragment of D15 protein [truncated D15 (tD15)] was expressed as a fusion protein with glutathione S-transferase in Escherichia coli. The tD15 moiety was cleaved from glutathione S-transferase by using thrombin and purified to homogeneity. The purified sol. tD15 appeared to contain immunodominant protective epitope(s) against Hia and Hib, since rabbit antisera directed against tD15 were capable of protecting infant rats from Hia or Hib bacteremia. The ease of purifn. of sol. tD15, therefore, makes it a better candidate antigen than the full-length recombinant D15 which is produced as inclusion bodies in E. coli. Furthermore, both the purified tD15 fragment and a mixt. of tD15-derived peptides spanning amino acid residues 93 to 209 of the mature D15 protein were capable of inhibiting the protection against Hib conferred on infant rats by rabbit anti-tD15 antiserum, indicating that the protective epitopes of D15 may not be conformational. However, the **administration** of pooled rabbit immune sera raised against the same panel of peptides failed to protect infant rats from Hib infection.

L28 ANSWER 2 OF 11 CAPLUS COPYRIGHT 1999 ACS

AN 1997:560572 CAPLUS
DN 127:233288
TI Effect of lipid modification on the physicochemical, structural, antigenic and immunoprotective properties of **Haemophilus influenzae** outer membrane protein P6
AU **Yang, Yan-Ping**; Munson, Robert S., Jr; Grass, Susan; **Chong, Pele**; Harkness, Robin E.; Gisonni, Lucy; James, Olive; Kwok, Yan; **Klein, Michel H.**
CS Research Center, Pasteur Merieux, Connaught, Canada, North York, M2R 3T4, Can.
SO Vaccine (1997), 15(9), 976-987
CODEN: VACCDE; ISSN: 0264-410X
PB Elsevier
DT Journal
LA English
AB The outer membrane lipoprotein, P6 of **H. influenzae** was studied to det. the importance of the native palmitoyl moiety on its physicochem. and immunol. properties. A recombinant P6 (rP6) mol. devoid of lipidation signal sequence was expressed in Escherichia coli and its properties were compared to those of the palmitoylated protein purified from **H. influenzae**. The isoelec. point of rP6 was more acidic than that of the native protein and also exhibited less secondary structure than P6 as judged by CD. However, both forms of P6 induced identical P6-specific antibody titers in guinea pigs when Freund's adjuvant was used. These antisera reacted with a panel of overlapping P6 peptides in a comparable manner and in addn., rabbit antisera raised against the P6 peptides reacted equally well with P6 and rP6. Furthermore, all human convalescent sera tested exhibited similar anti-P6 and anti-rP6 antibody titers. However, rP6 was less immunogenic than P6 when **administered** either without adjuvant or in alum and when tested in competitive inhibition studies with anti-P6 antibodies, was a less effective inhibitor than native P6, suggesting a diminution in some of the antigenic activity of rP6. In spite of these differences, rP6 was capable of eliciting a protective antibody response against live **H. influenzae** type b challenge in a modified infant rat model of bacteremia. Thus, the non-fatty acylated rP6 could possibly be substituted for native P6 in a vaccine against **H. influenzae**.

L28 ANSWER 3 OF 11 CAPLUS COPYRIGHT 1999 ACS
AN 1997:463653 CAPLUS
DN 127:113174
TI Immunogenicity of **Haemophilus influenzae** proteins encapsulated within biodegradable microparticles
AU Sokoll, Ken; Pszczolko, Helena; Frank, Peter; Hu, Jian; **Yang, Yan-Ping**; **Chong, Pele**; **Klein, Michel**
CS Research Centre, Pasteur Merieux Connaught Canada, Willowdale, ON,

M2R 3T4, Can.
SO Proc. Int. Symp. Controlled Release Bioact. Mater. (1997), 24th, 421-422
CODEN: PCRMEY; ISSN: 1022-0178
PB Controlled Release Society, Inc.
DT Journal
LA English
AB The humoral response to terpolymer (PLGpZS and PLGpS)-microencapsulated Hin-47 (**Haemophilus influenzae** proteins) can be substantially increased when **administered** via parenteral or mucosal routes. The quality of the immunogenic response (presentation of antigen) is influenced as indicated by differences with the IgG subtypes elicited. Mucosal immunization with antigen encapsulated microparticles has been shown to elicit moderate levels of sIgA. This has implications for the use of microparticles-based delivery systems for the induction of local protection at mucosal surfaces, as this is most often assocd. with sIgA in local secretions.

L28 ANSWER 4 OF 11 CAPLUS COPYRIGHT 1999 ACS
AN 1997:18360 CAPLUS
DN 126:46316
TI Cloning and expression of 200 kilodalton outer membrane protein gene of Moraxella catarrhalis and vaccines for **otitis media**
IN Sasaki, Ken; Harkness, Robin E.; **Loosmore, Sheena M.**; **Chong, Pele; Klein, Michel H.**
PA Connaught Laboratories Limited, Can.; Sasaki, Ken; Harkness, Robin E.; Loosmore, Sheena M.; Chong, Pele; Klein, Michel, H.
SO PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9634960	A1	19961107	WO 96-CA264	19960429
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	US 5808024	A	19980915	US 95-478370	19950607
	AU 9653941	A1	19961121	AU 96-53941	19960429
	EP 826052	A1	19980304	EP 96-910872	19960429
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

JP 11502415 T2 19990302 JP 96-532876 19960429
PRAI US 95-431718 19950501
US 95-478370 19950607
US 96-621944 19960326
WO 96-CA264 19960429

AB An isolated and purified outer membrane protein (OMP) of a Moraxella strain, particularly M. catarrhalis, having a mol. mass of about 200 kDa, is provided. The about 200 kDa OMP as well as nucleic acid mols. encoding the same are useful in diagnostic applications and immunogenic compns., particularly for in vivo **administration** to a host to confer protection against disease caused by a bacterial pathogen that produces the about 200 kDa OMP or produces a protein capable of inducing antibodies in a host specifically reactive with the about 200 kDa OMP. The gene for the OMP was cloned and sequenced. The 200 kDa OMP was almost always present in Moraxella strains isolated from patients suffering from **otitis media**. Antibodies specific for this protein were identified in serum from a convalescent patient having recovered from **otitis media** due to M. catarrhalis. Immunization of guinea pigs with an internal fragment of this protein generated antibodies which recognizes the 200 kDa protein.

L28 ANSWER 5 OF 11 CAPLUS COPYRIGHT 1999 ACS
AN 1996:137694 CAPLUS
DN 124:173429
TI Adjuvant compositions comprising a mineral salt and another immunostimulating compound
IN Kandil, Ali; James, Olive A.; **Chong, Pele**; **Klein, Michel H.**
PA Cannaught Laboratories Ltd., Can.
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9534308	A2	19951221	WO 95-CA359	19950615
WO 9534308	A3	19960523		
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5837250	A	19981117	US 95-483856	19950607
CA 2192659	AA	19951221	CA 95-2192659	19950615
AU 9526670	A1	19960105	AU 95-26670	19950615

EP 765163 A2 19970402 EP 95-921672 19950615
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
PRAI US 94-261194 19940616
WO 95-CA359 19950615
OS MARPAT 124:173429
AB Adjuvant compns. for modulating an immune response to an antigen **administered** to a host comprise a mineral salt adjuvant and at least one other adjuvant. The compns. provide an adjuvanting effect on an antigen which is greater than the adjuvanting effect attainable by one of the adjuvants alone. An antigen is covalently bonded to a glycolipid analog to provide a discrete mol. which exhibits an enhanced adjuvanting effect on the antigen which is greater than the adjuvanting effect attainable in the absence of such covalent bonding. The antigen is microbial pathogens, bacteria, viruses, proteins, glycoproteins, lipoproteins, peptides, glycopeptides, toxoids, carbohydrates, tumor-specific antigens, etc. In example, synthetic peptides were prepd. as antigen, and N-(2-L-leucine-amino-2-deoxy-.beta.-D-glucopyranosyl)-N-octadecyldodecanamide acetate, tripalmityl-Cys-Ser-Ser-Asn-Ala, tripalmityl-Cys-Ser-Glu-Glu-Glu-Glu, tripalmityl-Cys-Ser-Lys-Lys-Lys-Lys, etc. were prepd. as adjuvant. Formulations contg. these synthetic antigen and adjuvants were prepd. as vaccines for HIV, flu, RSV, PIV3, flu BHA, pertussis toxoid, etc.

L28 ANSWER 6 OF 11 MEDLINE
AN 1998453011 MEDLINE
DN 98453011
TI Study on **Haemophilus influenzae** type b diseases in China: the past, present and future.
AU **Yang Y**; Shen X; Jiang Z; Liu X; Leng Z; Lu D; Rao J; Liu J; Chang L
CS Laboratory of Microbiology and Immunology, Beijing Children's Hospital, China.
SO PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1998 Sep) 17 (9 Suppl) S159-65.
Journal code: OXJ. ISSN: 0891-3668.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB Meningitis caused by **Haemophilus influenzae** type b (Hib) is a common and serious disease for which there now are WHO-certified vaccines that are recommended for universal infant immunization in North America and European countries. If these vaccines are to be recommended in Asia, it is necessary to know the incidence, age distribution and clinical outcome of Hib meningitis

and other systemic infections in this region. Data on Hib disease in China are scanty. Hib meningitis was common during the 1950s in China, accounting for up to 16% of all of pyogenic meningitis (up to 38% of cases were caused by unknown pathogens), despite severe epidemics of meningococcal meningitis during that period. Since 1989 we have conducted hospital- and community-based etiologic and epidemiologic studies of bacterial meningitis. Hib accounts for 30 to 50% of bacterial meningitis in China. The incidence of Hib meningitis in Hefei City was 10.4 per 100000 children <5 years, a result relatively lower than in the West but higher than the rate of 2.7 found in a retrospective study in Hong Kong. Pneumonia is the primary cause of death for Chinese children. From 1991 to 1993 the average mortality of children<5 years because of pneumonia was 1563.2 per 100000. To achieve the goal of reducing the death rate of children by one-third by the year 2000, greater efforts should be made to reduce the mortality of children with pneumonia. Our preliminary study showed that about one-fourth to one-third of cases of pneumonia in Chinese children might be caused by Hib. Therefore Hib vaccination for infants and children in China might be an effective and valuable procedure to achieve the goal.

L28 ANSWER 7 OF 11 MEDLINE
AN 95312349 MEDLINE
DN 95312349
TI Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood. International Study Group.
AU **Klein M**
CS Department of Paediatrics and Child Health, University of Cape Town, South Africa.
SO PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1995 Apr) 14 (4 Suppl) S19-22.
Journal code: OXJ. ISSN: 0891-3668.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 199509
AB Acute lower respiratory tract infections in children are a worldwide public health problem, with an estimated 4 million potentially preventable deaths every year. Until recently, penicillin and related drugs were the treatment of choice for empiric therapy of paediatric lower respiratory tract infections. However, concerns over the emergence of penicillin-resistant strains of Streptococcus pneumoniae and beta-lactamase-producing strains of **Haemophilus influenzae** and Moraxella catarrhalis

have led physicians to turn increasingly towards alternatives, such as the third generation cephalosporins. The oral extended spectrum cephalosporin cefpodoxime proxetil is highly active against the bacterial pathogens commonly associated with childhood lower respiratory tract infections. In order to evaluate its clinical efficacy in children with acute febrile lower respiratory tract infections, an international, multicenter, comparative, randomized open study was conducted in children ages 3 months to 11.5 years. Of 348 cases enrolled, 234 were randomized to cefpodoxime proxetil (8 mg/kg/day twice daily) and 114 to amoxicilin/clavanulate (amoxicillin 40 mg/kg/day 3 times a day). The duration of treatment was 10 days. Pretreatment diagnosis was pneumonia in 292 patients, bronchiolitis in 19 patients and acute bronchitis in 37 patients. Pathogens isolated from 59 cases included **H. influenzae** (47.5%), S. pneumoniae (23.7%), M. catarrhalis (11.9%) and Haemophilus parainfluenzae (6.8%). Clinical efficacy was evaluable in 278 children at the end of treatment when 95.2% of patients in the cefpodoxime proxetil group and 96.7% of patients in the amoxicillin/clavanulate group showed a satisfactory clinical response (cured or improved). The improvement was sustained at the follow-up visit, 10 to 20 days after completion of treatment.(ABSTRACT TRUNCATED AT 250 WORDS)

L28 ANSWER 8 OF 11 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 95121497 EMBASE
DN 1995121497
TI Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood.
AU **Klein M.**
CS Dept. of Paediatrics/Child Health, University of Cape Town, Red Cross War Memorial Child. Hosp., Klipfontein Road,7700 Rondebosch, South Africa
SO Pediatric Infectious Disease Journal, (1995) 14/4 SUPPL. I (S19-S22).
ISSN: 0891-3668 CODEN: PIDJEV
CY United States
DT Journal; Conference Article
FS 007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
LA English
SL English
AB Acute lower respiratory tract infections in children are a worldwide public health problem, with an estimated 4 million potentially preventable deaths every year. Until recently, penicillin and related drugs were the treatment of choice for empiric therapy of paediatric lower respiratory tract infections. However, concerns over the emergence of penicillin-resistant strains of Streptococcus pneumoniae and beta-lactamase-producing strains of

Haemophilus influenzae and Moraxella catarrhalis have led physicians to turn increasingly towards alternatives, such as the third generation cephalosporins. The oral extended spectrum cephalosporin cefpodoxime proxetil is highly active against the bacterial pathogens commonly associated with childhood lower respiratory tract infections. In order to evaluate its clinical efficacy in children with acute febrile lower respiratory tract infections, an international, multicenter, comparative, randomized open study was conducted in children ages 3 months to 11.5 years. Of 348 cases enrolled, 234 were randomized to cefpodoxime proxetil (8 mg/kg/day twice daily) and 114 to amoxicilin/clavanulate (amoxicillin 40 mg/kg/day 3 times a day). The duration of treatment was 10 days. Pretreatment diagnosis was pneumonia in 292 patients, bronchiolitis in 19 patients and acute bronchitis in 37 patients. Pathogens isolated from 59 cases included **H. influenzae** (47.5%), S. pneumoniae (23.7%), M. catarrhalis (11.9%) and Haemophilus parainfluenzae (6.8%). Clinical efficacy was evaluable in 278 children at the end of treatment when 95.2% of patients in the cefpodoxime proxetil group and 96.7% of patients in the amoxicillin/clavanulate group showed a satisfactory clinical response (cured or improved). The improvement was sustained at the follow-up visit, 10 to 20 days after completion of treatment. There was no difference in bacteriologic efficacy of the two treatments, and both drugs were well-tolerated. Thus cefpodoxime proxetil is highly effective and well tolerated in childhood pneumonia and is at least as effective as the comparator drug.

L28 ANSWER 9 OF 11 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-06952 BIOTECHDS
TI New non-denatured transferrin receptor protein from Moraxella and related antibodies;
Moraxella catarrhalis transferrin receptor monoclonal antibody production and hybridoma cell culture construction
AU **Yang Y P**; Myers L E; Harkness R E; **Klein M H**
PA Connaught-Lab.
LO North York, Ontario, Canada.
PI WO 9713785 17 Apr 1997
AI WO 96-CA684 11 Oct 1996
PRAI US 95-540753 11 Oct 1995
DT Patent
LA English
OS WPI: 97-235839 [21]
AN 97-06952 BIOTECHDS
AB An isolated and purified non-denatured transferrin receptor protein of a Moraxella strain (preferably Moraxella catarrhalis and especially M. catarrhalis 4223, 5191 or 135) having an apparent mol.wt. of about 80,000-90,000 as determined by SDS-PAGE, a fragment or an analog is claimed. Also claimed are antibodies raised against the transferrin receptor. A method (claimed) for

producing monoclonal antibodies specific for the transferrin receptor involves: (a) **administering** the transferrin receptor protein to at least one mouse to produce at least one immunized mice; (b) removing B-lymphocytes from at least one immunized mouse; (c) fusing the B-lymphocytes from the immunized mouse with myeloma cells, thereby producing hybridomas; (d) cloning the hybridomas; (e) selecting the clones which produce anti-transferrin receptor protein antibody; (f) culturing the anti-transferrin receptor protein antibody-producing clone; and (g) isolating anti-transferrin receptor protein antibodies from the cultures. The antibodies may be used in the diagnostic detection of the transferrin receptor, e.g. to differentiate Moraxella sp. from other bacteria that cause **otitis media**.- (57pp)

L28 ANSWER 10 OF 11 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 94:11260 SCISEARCH
GA The Genuine Article (R) Number: MM453
TI BRANHAMELLA-CATARRHALIS PATHOGENESIS IN SCID AND SCID/BEIGE MICE
AU HARKNESS R E; GUIMOND M J; MCBEY B A; **KLEIN M H**; PERCY D H; CROY B A (Reprint)
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB SCID and SCID/beige mice were used to study the pathogenesis of B. catarrhalis **administered** by intranasal, intraperitoneal or intravenous routes. Challenged adult animals did not appear overtly clinically ill. Similar symptoms were observed regardless of the challenge route, and pretreatment of mice with human transferrin did not enhance clinical virulence. Susceptibility to B. catarrhalis appeared to be age-dependent as some mice under one week of age died following challenge. Postmortem findings included circumscribed pale foci on the liver, splenomegaly and mineralization of the myocardium. Presence of lesions did not correlate with the assessment of clinical well being, and severity of the lesions was found to be challenge strain-dependent. Liver lesions and splenomegaly were not observed in animals challenged with heat-killed bacteria or placebo. SCID/beige mice were more affected than SCID mice both clinically and pathologically, suggesting that

natural killer cell and polymorphonuclear cell functions may be important in resolving B. catarrhalis challenge.

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TI Multicenter trial of cefpodoxime proxetil vs. amoxicillin-clavulanate in acute lower respiratory tract infections in childhood. International Study Group.
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AB Acute lower respiratory tract infections in children are a worldwide public health problem, with an estimated 4 million potentially preventable deaths every year. Until recently, penicillin and related drugs were the treatment of choice for empiric therapy of paediatric lower respiratory tract infections. However, concerns over the emergence of penicillin-resistant strains of Streptococcus pneumoniae and beta-lactamase-producing strains of **Haemophilus influenzae** and Moraxella catarrhalis have led physicians to turn increasingly towards alternatives, such as the third generation cephalosporins. The oral extended spectrum cephalosporin cefpodoxime proxetil is highly active against the bacterial pathogens commonly associated with childhood lower respiratory tract infections. In order to evaluate its clinical efficacy in children with acute febrile lower respiratory tract infections, an international, multicenter, comparative, randomized open study was conducted in children ages 3 months to 11.5 years. Of 348 cases enrolled, 234 were randomized to cefpodoxime proxetil (8 mg/kg/day twice daily) and 114 to amoxicilin/clavanulate (amoxicillin 40 mg/kg/day 3 times a day). The duration of treatment was 10 days. Pretreatment diagnosis was pneumonia in 292 patients, bronchiolitis in 19 patients and acute bronchitis in 37 patients. Pathogens isolated from 59 cases included **H. influenzae** (47.5%), S. pneumoniae (23.7%), M. catarrhalis (11.9%) and Haemophilus parainfluenzae (6.8%). Clinical efficacy was evaluable in 278 children at the end of treatment when 95.2% of patients in the cefpodoxime proxetil group and 96.7% of patients in

the amoxicillin/clavanulate group showed a satisfactory clinical response (cured or improved). The improvement was sustained at the follow-up visit, 10 to 20 days after completion of treatment. (ABSTRACT TRUNCATED AT 250 WORDS)

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